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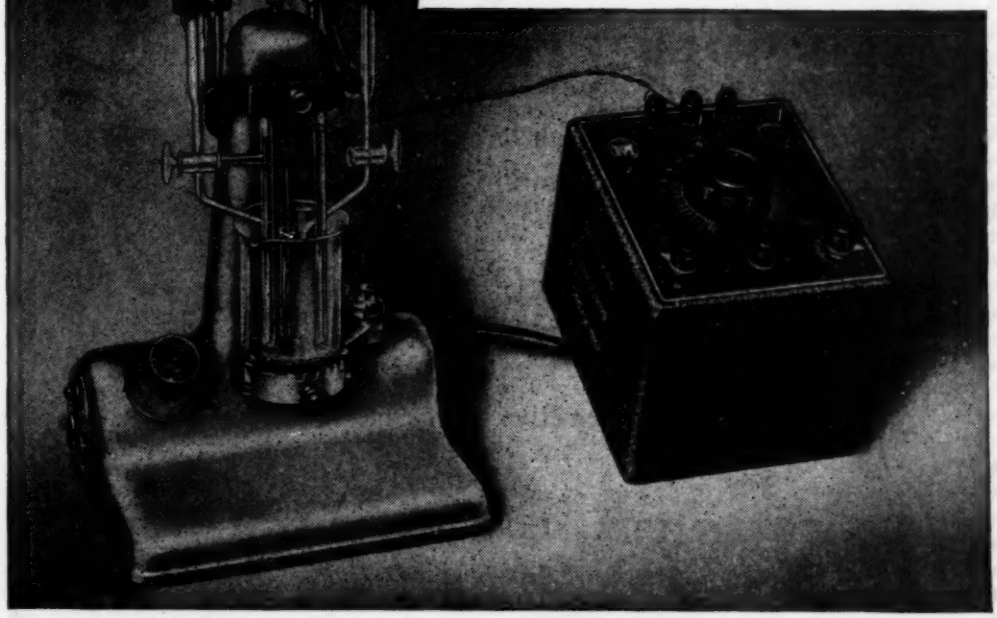

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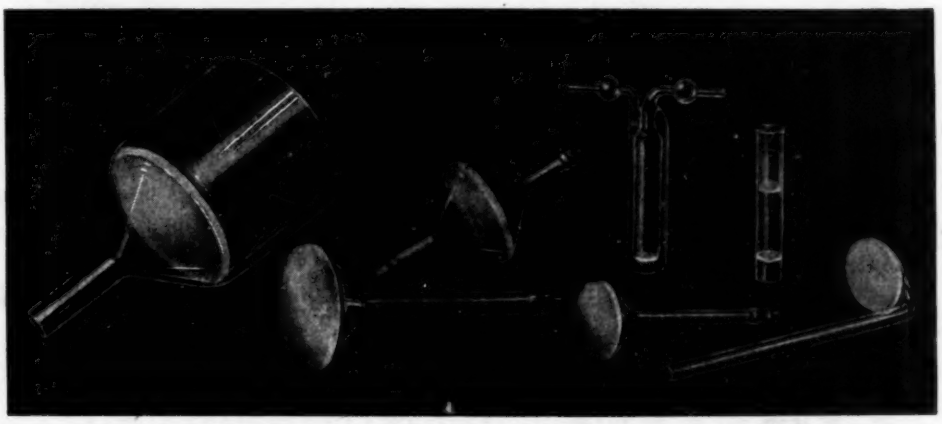

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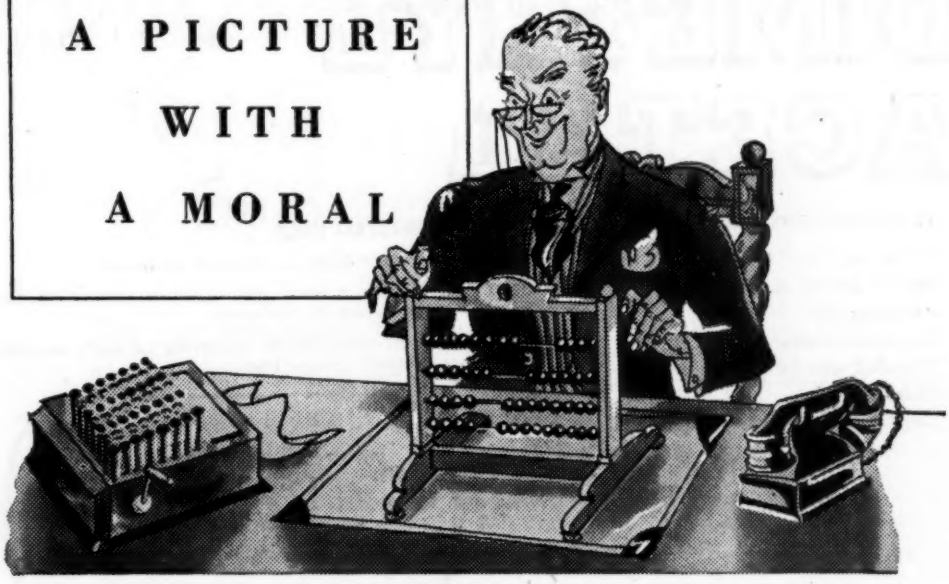

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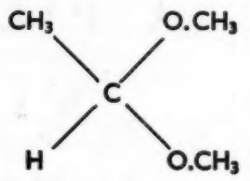

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135. *Tetra-acetyl Glucosone Hydrate. A Novel Route to the Syntheses of Analogues of Ascorbic Acid and a Possible Mechanism for the Transformation of Hexoses into Kojic Acid.*

By M. Stacey and Lilian M. Turton.

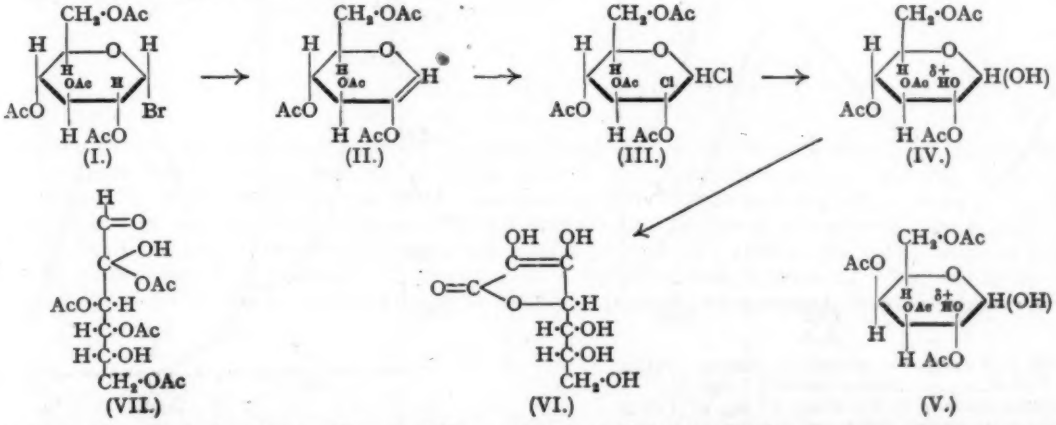
A reinvestigation of the reactions of tetra-acetyl glucosone hydrate has given support to Maurer's formulation of it as 2 : 3 : 4 : 6-tetra-acetyl glucosone hydrate (IV). The compound possesses one incipiently ionic hydrogen atom and forms a *monomethyl* and a dimethyl *ether*. It provides convenient initial material for the syntheses of analogues of ascorbic acid by two routes. Observations have been made on the absorption spectra of kojic acid and related substances and a mechanism for the conversion of (IV) and its hexose analogues into kojic acid is suggested.

Maurer (*Ber.*, 1929, **62**, 332; 1930, **63**, 25; Maurer and Petsch, *Ber.*, 1931, **64**, 2011) has described the synthesis from glucose of a remarkable crystalline glucosone derivative which he formulated as 2 : 3 : 4 : 6-tetra-acetyl glucosone hydrate (IV). The steps in his synthesis were as follows:

Penta-acetyl glucose $\xrightarrow[\text{acetic acid}]{\text{HBr in}}$ acetobromoglucose (I) $\xrightarrow{\text{diethylamine}}$ 2 : 3 : 4 : 6-tetra-acetyl 1 : 2-glucosene (II) $\xrightarrow{Cl_2}$ 1 : 2-dichloro 3 : 4 : 6-triacetyl 2-acetoxy glucal (III) $\xrightarrow{Ag_2CO_3}$ 2 : 3 : 4 : 6-tetra-acetyl glucosone hydrate (IV).

In a similar manner an analogous compound, 2 : 3 : 4 : 6-tetra-acetyl galactosone hydrate (V), was obtained from galactose (Maurer and Müller, *Ber.*, 1930, **63**, 2069). Both of these compounds on being treated with acetic anhydride in pyridine lost two molecules of acetic acid and underwent an intramolecular change with loss of configuration to form diacetyl kojic acid (XX).

Since osones have proved of considerable value as initial material for the syntheses of analogues of ascorbic acid, and because some points in regard to the structure of hexosone hydrates were still obscure, it was deemed of interest to reinvestigate Maurer's compound.



As it was clear that the stages (II) ⟶ (III) ⟶ (IV) entailed an oxidation process, a reagent was sought which would accomplish the conversion of (II) ⟶ (IV) in one step. Perbenzoic acid was found to be eminently suitable since by its action in ethereal solution (II) was converted in *ca.* 30% yield into a crystalline substance of m. p. 151°, $[\alpha]_D$ + 8° in ethanol. Although these properties of (IV) differed from those recorded by Maurer (m. p. 118°, $[\alpha]_D$ + 14° ⟶ + 55°) there would appear to be no doubt that we had obtained (IV) in a highly purified form. Thus it reduced Fehling's solution in the cold, it rapidly decolorised potassium permanganate, and after cautious deacetylation and treatment with phenylhydrazine in the cold it gave glucose phenylosazone. On acetylation at room temperature with acetic anhydride in pyridine it was converted in 80% yield into diacetyl kojic acid (XX) which was identical with diacetyl kojic acid prepared from the kojic acid of *Aspergillus oryzæ*. The synthetic diacetyl kojic acid could be smoothly deacetylated to authentic kojic acid (XV).

Conclusive proof of the structure of (IV) as a derivative of glucosone was furnished by the fact that on treatment in aqueous solution with potassium cyanide and calcium chloride, using the method of Baird *et al.* (*J.*, 1934, **62**), it was converted into glucoascorbic acid (VI). The alkaline reagents effected deacetylation, the course of the reaction could be followed iodometrically and spectrophotometrically, and the yield of glucoascorbic acid was reasonably high. It is known that hexosones can be directly oxidised with hypobromous acid to 2-keto hexonic acids (Neuberg and Kitasato, *Biochem. Z.*, 1927, **183**, 485). Since the success of this method depends upon the purity of the hexosones (F. Smith, "Advances in Carbohydrate Chemistry," in the press) it would seem that the crystalline tetra-acetyl hexosone hydrates form eminently suitable material for the syntheses of analogues of ascorbic acid by two routes. In our hands an oxidation of (IV) with bromine

water, followed by heating of the oxidation product with acid, gave a substance in solution which reduced ammoniacal silver nitrate at room temperature and had an absorption band at λ 2450 A., but on the small scale on which the reaction was carried out the *d*-araboascorbic acid which was probably produced was not isolated in crystalline form.

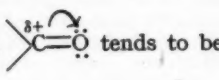
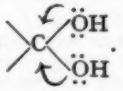
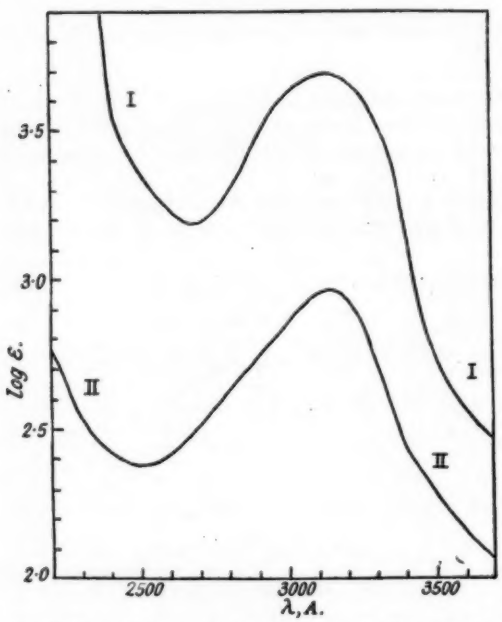
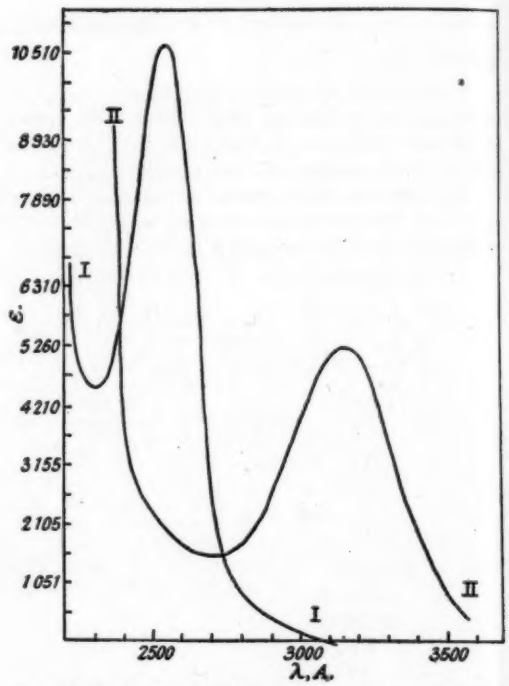
In reactions leading to the synthesis of ascorbic acid analogues the tetra-acetyl glucosone hydrate evidently reacts in the acyclic form (VII), and it is of interest to inquire into the reasons for the stability of such hexosone derivatives and to note the conditions under which  tends to become hydrated to  . The best known example is the conversion of chloral into the relatively stable chloral hydrate. Certain halogenated ketones, in particular trifluoroacetyl derivatives (Swartz, *Bull. Sci. Acad. Roy. Belge*, **1927**, **13**, 175; Stacey and Turton, unpublished results), have been observed to behave similarly. It would appear that when an electrophilic group (R) is attached to the carbonyl group the latter tends to be modified so that it no longer is an acceptor of electrons. Such a condition would appear to obtain in tetra-acetyl glucosone

FIG. 1.

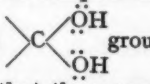


I. *Kojic acid in aqueous neutral or alkaline solution* (λ 3150 A., $\epsilon_{max.}$ ca. 5000; *concn.* 3·7 *mg.*-%).
II. *Solution obtained by dissolving* 2·7 *mg. of* (IV) *in* 0·5 *c.c. of boiling* 0·67N-*sodium hydroxide and diluting to* 90 *mg.*-% *with water* (λ 3150A., $\epsilon_{max.}$ ca. 850).

FIG. 2.



I. *Diacetylkojic acid* (*concn.* 4·3 *mg.*-% *in water*; λ 2550 A., ε ca. 10,000).
II. *Solution I made alkaline* (λ 3150A., ε ca. 5000).

hydrate. When, in such compounds, the electron attracting property of the group (R) can be satisfied by some other means, the  group will be rendered unstable and will tend to revert to the ketonic form. It will be seen below that these arguments are pertinent in considering the formation of the keto group in kojic acid (cf. Isbell, *Ann. Rev. Biochem.*, **1943**, **12**, 205; *N.B.S. U.S.A. J. Res.*, **1944**, **32**, 45).

There have been but few investigations conducted with the object of interpreting transformations in the carbohydrate group in terms of the electronic theory, though there have been recently some attractive suggestions along these lines in regard to well-known reactions. In particular Isbell (**1944**, *loc. cit.*) has suggested a mechanism to explain the formation of diacetyl kojic acid from (IV). Our experimental observations agree in some measure with this author's theoretical considerations, but we do not consider that some of his postulations, particularly those envisaging the formation of ortho-acetate structures, are necessary since even simple alkali treatment converts (IV) into (XV) (see Fig. 1, curves I and II).

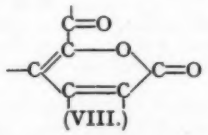
Kojic acid is of some considerable biological interest for it can be produced in high yields by various mould species such as *A. oryzæ* (Challenger, Klein, and Walker, *J.*, **1929**, **1498**) not only from disaccharides but also from pentoses, tetroses, etc., and even from glycerol as the sole source of carbon. Its formulation as a γ-pyrone (XV) was worked out by Yabuta (*J.*, **1924**, **125**, 575) though its derivatives have as yet been but

little investigated. It is unlikely that the mechanism of its formation from (IV) will have any bearing on the biological mode of synthesis.

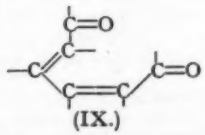
Acetyl determinations on (IV) using the method of adding excess sodium hydroxide followed by back titration (cf. Maurer, *loc. cit.*) indicated the apparent presence of five acetyl residues, whereas acetyl estimations by determining the volatile acetic acid liberated on acid hydrolysis revealed only four. The reason for the discrepancy was clear when it was shown that titration of (IV) with sodium carbonate required one equivalent, thus indicating that one hydrogen atom could be liberated as a proton. Acidification of the solution containing the sodio derivative followed by ether extraction recovered (IV) unchanged. Methylation of (IV) with silver oxide and methyl iodide gave a crystalline *monomethyl ether*, together with a syrupy product which was essentially a dimethyl ether, thus showing that (IV) possessed two free hydroxyl groups. These facts can all be accommodated by the structure (IV) or by the less likely acyclic structure (VII).

Spectrophotometric measurements have provided strong additional evidence for the readiness with which the glucosone derivative is converted into kojic acid. Fig. 1 (curve II) shows the ultra-violet absorption of a solution obtained by treatment with aqueous alkali of (IV) which itself in neutral solution does not absorb light selectively. For comparison the absorption curve of an authentic specimen of mould kojic acid is given in Fig. 1 (curve I). In Fig. 2 (curve I) is shown the ultra-violet absorption of the product obtained by acetylating (IV) with acetic anhydride in pyridine. That this was a diacetyl kojic acid was confirmed by the fact that, after treatment with alkali, it gave an absorption band (Fig. 2, curve II) identical with that of authentic kojic acid.

In connection with these absorption curves it is of interest to draw attention to some observations made on certain other ketonic compounds (cf. Haworth, Hirst, and Jones, *J.*, 1938, 710; Haworth, Heslop, Salt, and Smith, *ibid.*, 1944, 217). In particular 6-carbomethoxy-3-methoxy-α-pyrone shows a band at λ 3070 A., $\epsilon_{max.}$ 12,000, and dimethyl 2 : 5-dimethoxymuconate (obtained by alkaline treatment of a methyl tetramethylglucosaccharate, L. F. Wiggins, private communication) has a maximum absorption at λ 3020 A., the intensity varying with the concentration (*e.g.*, *c*, 1·65 mg.-%, ε 25,000). In these cases the absorbing systems must be (VIII) and (IX) respectively.

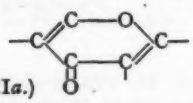


(VIII.)

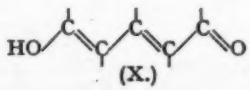


(IX.)

Comparable with the band shift between the neutral and alkaline solutions of diacetyl kojic acid are the values found for the absorption maxima of the mono-enol of 3 : 7-diketocholestene (Barnett, Ryman, and Smith, this vol., p. 526) in ethanolic solution. The monoacetate of this enol displays a band at λ 2840 A., log ε 4·4, in neutral solution and on making the solution alkaline this band moves to λ 3900 A., log ε 4·78. The unsubstituted enol and its ethers show a maximum absorption at λ 3120 A., log ε 4·4, which in the case of the enol itself is displaced in alkali to λ 3900 A. with a slight increase in intensity. The similarity in the position of the band to that of kojic acid is quite striking; the absorbing system in kojic acid is (VIII*a*),

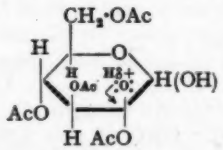


(VIII*a*.)

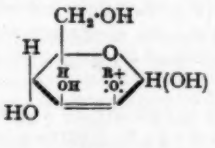


(X.)

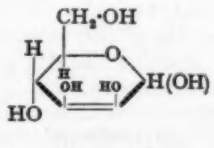
while in the sterol derivative it is presumably (X).



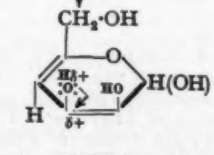
(IV.)



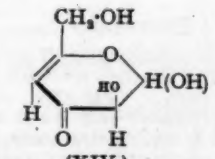
(XI.)



(XII.)

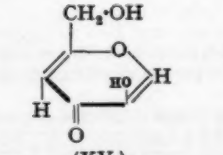


(XIII.)



(XIV.)

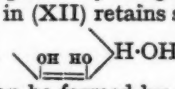
(R⁺ = *e.g.*, Na⁺).

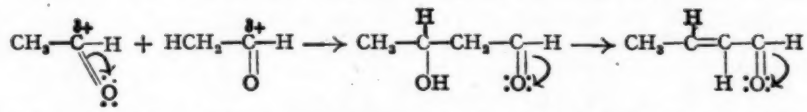


(XV.)

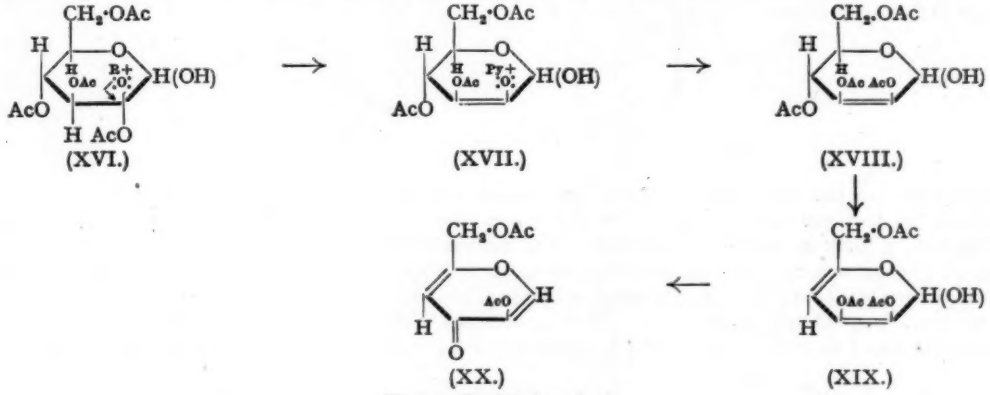
It is considered that treatment of (IV) with aqueous alkali, in addition to effecting deacetylation, will neutralise on C_2 the hydrogen atom which is incipiently ionic (cf. VII). The transformation of (IV) then

probably proceeds in the initial stages essentially as suggested by Isbell (1944, *loc. cit.*) involving a loss of water between C_3 and C_2 with formation of the ene-diol (XI). From this stage we disagree with Isbell's mechanism inasmuch as we consider that a proton acceptor group (*e.g.*, hydroxyl or pyridine) is essential to promote the successive stages such as the conversion (IV) ⟶ (XII). In aqueous solution R^+ in (XI) would readily be replaced by H^+ giving (XII).

Since C_1 in (XII) retains some of the reducing properties of a free aldehyde group (as in all reducing sugars) the system  is in effect analogous to the "ene-one" system in crotonaldehyde. This substance can be formed by an aldol condensation by a mechanism similar to the one leading to (XII) thus:



Crotonaldehyde may undergo further condensation because there is an electron drift towards the CHO group and thus the linkage of the hydrogen atoms to C_4 becomes less firm. In the same way the linkages of both the hydrogen atom and the hydroxyl group on C_4 in (XII) are weakened. Formation of (XIII) by loss of water between C_4 and C_5 can remedy this since there results thereby a conjugated system in which there is a possibility of resonance. As in crotonaldehyde, the aldehydic carbon, C_1, will retain electron acceptor properties and this will cause a tendency in the hydrogen of the C_3 enolic group to ionise with the possible intermediate formation of (XIV). Alternatively the proton may attack directly the aldehydic hydroxyl group on C_1 with the result that kojic acid (XV) is formed. Such a mechanism is independent of the geometry of the hydroxyl groups in respect to the ring and thus, as already shown experimentally in the case of tetra-acetyl galactosone hydrate, the interpretation will hold for any hexosone derivative.



(XVI.) (XVII.) (XVIII.) (XIX.) (XX.)

(Py^+ = Pyridinium ion)

In the acetylation reactions in pyridine solution the transformation is less simple though a similar interpretation is possible. In pyridine–acetic anhydride solution there can be a donation of electrons by the pyridine to the incipiently ionic proton on C_2 (XVI) followed by loss of acetic acid between C_2 and C_3 giving the acetylated ene-diol (XVII). From this the pyridinium ion will be removed by acetic acid to form (XVIII). A further loss of one molecule of acetic acid by the electronic mechanism suggested above for the transformation in aqueous solution gives (XIX), and finally by loss of a third molecule of acetic acid there results diacetyl kojic acid (XX).

A somewhat similar mechanism has been suggested by Isbell (1943, *loc. cit.*) for the formation by means of acetic anhydride–pyridine treatment of 1 : 2 : 3 : 5-tetra-acetoxybenzene from both of two ketopentaacetates derived from oxidised inositol. Here Isbell again does not specify that a proton acceptor must be used to promote the reaction whereas we regard this as one of the essential factors in such a transformation.

Experimental.

2 : 3 : 4 : 6-*Tetra-acetyl* 1 : 2-*Glucosene*.—Acetobromoglucose (62 g.) was dissolved in benzene according to the method of Maurer and Mahn (*Ber.*, 1927, **60**, 1316). The product was recrystallised by dissolving it in warm alcohol, then adding a few drops of water and agitating vigorously. Yield 22 g., m. p. 61—62°.

Oxidation of Tetra-acetyl 1 : 2-*Glucosene*.—Perbenzoic acid (14 g. in 200 c.c. of ether) was prepared from benzoyl peroxide by the method of Tiffeneau (*Org. Synth.*, **8**, 30). Tetra-acetyl 1 : 2-glucosene (22·5 g.) was added to the ethereal solution which was cooled in ice and shaken until all the solid was dissolved. After 20 hours there separated a crystalline substance which was washed repeatedly on the filter with ether to remove perbenzoic and benzoic acids and then dried. It was recrystallised several times from water and had m. p. 150—151°. From the mother liquor there were separated several further crops of this material giving a total yield of 6·0 g. An unidentified substance having m. p. 93° was separated from the final mother liquor. The main bulk of material had m. p. 151°, $[\alpha]_D^{20°}$ + 8·4° in 20% aqueous alcohol (*c*, 1·3) [Found : C, 46·3; H, 5·5. Calc. for tetra-acetyl glucosone hydrate $C_{14}H_{20}O_{11}$: C, 46·2; H, 5·5%. *O*-Ac (by direct

titration), 59·7; *O*-Ac (by an acid distillation), 52·0. Calc. for 4 *O*-Ac residues : *O*-Ac, 47·3; for 5 *O*-Ac residues, *O*-Ac, 59·1%. Replaceable hydrogen (titration with 0·05N-sodium carbonate), 2·77. Calc. for $C_{14}H_{22}O_{11}$ containing one replaceable hydrogen : 2·74%. On acidification of the titrated solution, followed by extraction with ether, tetra-acetyl glucosone hydrate was recovered unchanged].

Methylation of Tetra-acetyl Glucosone Hydrate.—The hydrate (3·0 g.) was methylated three times with silver oxide and methyl iodide in the usual manner. The product was extracted by chloroform and there was obtained a syrup which partly crystallised. Recrystallised from chloroform–ligroin the crystals (0·2 g.) had m. p. 120°, $[\alpha]_D^{18°}$ + 20° in chloroform (*c*, 1·0) (Found : C, 47·6; H, 5·8; OMe, 8·5. *Monomethyl tetra-acetyl glucosone hydrate*, $C_{15}H_{22}O_{11}$, requires C, 47·6; H, 5·8; OMe, 8·2%). The syrupy residue had OMe, 14·6% (Calc. for dimethyl tetra-acetyl glucosone hydrate, $C_{16}H_{24}O_{11}$: OMe, 15·8%).

Conversion of Tetra-acetyl Glucosone Hydrate into Diacetyl Kojic Acid.—The hydrate (3·0 g.) was shaken with pyridine (20 c.c.) and acetic anhydride (20 c.c.) and then kept at room temperature for 3 days. The solvents were then distilled off under diminished pressure at 35° and the solid residue was recrystallised (1·3 g.) from alcohol–ligroin to constant m. p. 103° alone or in admixture with a specimen prepared by acetylating with the same reagents a specimen of kojic acid obtained from glucose with *A. oryzæ*. On treatment with ammonia both the synthetic and the mould specimen of diacetyl kojic acid were smoothly deacetylated to kojic acid, m. p. 153° alone or in admixture with a specimen from *A. oryzæ*.

Synthesis of Glucoascorbic Acid from Tetra-acetyl Glucosone Hydrate.—Tetra-acetyl glucosone hydrate (4 g.) was dissolved in oxygen-free hot water (250 c.c.) and cautiously cooled (avoiding crystallisation) to 37°. To the solution potassium cyanide (2·5 g.) and calcium chloride (3 g.) were added. Oxygen-free nitrogen was passed through the solution which was kept at room temperature. Titration of small portions from time to time with N/50-iodine showed that the reaction was complete in 1 hour. The calcium was removed quantitatively as oxalate and the solution was acidified with dilute acetic acid and concentrated under diminished pressure in a stream of carbon dioxide to a syrup. This was dissolved in 8% hydrochloric acid (50 c.c.) and the solution digested at 50° for 20 hours; the head of the absorption band at λ 2750 A. was then completely replaced by a band at λ 2450 A. The product in solution was worked up as described previously (Baird, *et al.*, *loc. cit.*) and there resulted glucoascorbic acid monohydrate (1·5 g.), m. p. 138°, $[\alpha]_D^{19°}$ — 22° in methyl alcohol (*c*, 1·1 as monohydrate). After oxidation with iodine it gave a yellow phenylhydrazine derivative, m. p. 222°.

Oxidation of Tetra-acetyl Glucosone Hydrate with Bromine.—The glucosone hydrate (1 g.) was dissolved in boiling water (100 c.c.) and cautiously cooled to 40°, and bromine (0·5 g.) was added. The solution was kept at 40° for 30 hours; the last traces of bromine were then removed in a stream of nitrogen. The solution was concentrated (diminished pressure in carbon dioxide) to 50 c.c. Glacial acetic acid was added and the solution digested at 80° for 24 hours. On working up the product in the usual manner a syrup, $[\alpha]_D^{20°}$ — 20° (*c*, 0·6 in water), was obtained. This had a strong absorption band at λ 2450 A., reduced Fehling's solution readily, reduced ammoniacal silver nitrate in the cold, and after oxidation with iodine gave a yellow phenylhydrazine derivative, m. p. 200°.

Absorption Measurements.—The following data were obtained. (i) Kojic acid in aqueous neutral or alkaline solution : $\epsilon_{max.}$ *ca.* 5000, λ 3150 A. (*c.*, 3·7 mg.-%).

(ii) Tetra-acetyl glucosone hydrate shows no band in neutral solution. On dissolving 2·7 mg. in 0·5 c.c. of 0·67N-sodium hydroxide a deep yellow solution was obtained. This was diluted with water to *c*, 90 mg.-% and showed $\epsilon_{max.}$ *ca.* 850, λ 3150 A. The ε value is calculated assuming *M* to be 364 (*i.e.*, *M* of tetra-acetyl glucosone hydrate).

On keeping the solution (*c*, 90 mg.-%) for 2 hours the ε value had decreased to $\epsilon_{max.}$ *ca.* 700. Thus the absorbing substance was undergoing some decomposition.

6-Carbomethoxy-3-methoxy-α-pyrone (Haworth *et al.*, *loc. cit.*) shows a band at λ 3090 A., $\epsilon_{max.}$ 12,000 (*c*, 2·0 mg.-% in water).

It was difficult to show by ultra-violet absorption methods that pyridine alone would effect the transformation (IV) ⟶ (XV). Nevertheless when an alcohol–pyridine solution of (IV) was compared with alcohol–pyridine alone there was a slight modification in the region of λ 3000—3300 A. of the pyridine band.

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[*Received, December 20th*, 1945.]

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136. *Basic Derivatives of Cholane and Norcholane.*

By Sybil P. James, F. Smith, M. Stacey, and M. Webb.

The synthesis of certain basic nitrogen derivatives of cholane and norcholane is described. The hydrochlorides of 23-amino-3 : 7 : 12-trihydroxynorcholane (I) and 23-amino-3 : 12-dihydroxynorcholane (II) were made by the method of Caldwell and 23-*amino*-3 : 12-*dihydroxy*-Δ^{8}-*norcholene* (III) was similarly prepared from 3 : 12-*dihydroxy*-Δ^{8}-*cholenylhydrazine* while the decomposition of 3 : 12-*dihydroxy*-7-*ketocholanylhydrazine* 7-*hydrazone* (IV) afforded 23-*amino*-3 : 12-*dihydroxy*-7-*ketonorcholane hydrochloride* (V). Dehydration of triformylcholylamide gave 3 : 7 : 12-*triformyl*-23-*cyanonorcholane* from which 3 : 7 : 12-*trihydroxy*-23-*cyanonorcholane* (VII) was obtained. This was converted into 23-*amidino*-3 : 7 : 12-*trihydroxynorcholane hydrochloride* (VIII), 24-*amino*-3 : 7 : 12-*trihydroxycholane hydrochloride* (IX), and 3 : 7 : 12-triketo-23-cyanonorcholane (XI) which gave a *trioxime*. (I) and (IX) furnished the corresponding guanido-derivatives (VI) and (X). 7-Amino-3 : 12-dihydroxycholanic acid was obtained on reduction of the *oxime* of ethyl 3 : 12-dihydroxy-7-ketocholanate and was isolated as the *hydrochloride* (XII) and as the N-*benzoyl* derivative. Reduction of the trioxime derived from dehydrocholic acid and subsequent removal of the residual oxime group gave a *diamino-keto-acid dihydrochloride* (presumably 3 : 7-diamino-12-ketocholanic acid dihydrochloride, XIII).

The *in vitro* antibacterial action of the bile acids against certain Gram-positive micro-organisms is well known and the literature has been adequately reviewed by Sobotka (" Physiological Chemistry of the Bile," Baillière, Tindall, and Cox, 1937, 125). Attempts to use the bile acids for chemotherapeutic purposes, principally in the case of pneumococcus (White, " The Biology of Pneumococcus," New York, 1938, 507), have, however, been complicated by the toxicity, hæmolytic action, and destructive effect on leucocytes produced by these acids. With the object of preparing arsenical therapeutics of greater lipoid solubility than that of compounds previously employed, Lieb, Verdino, and Schadendorff (*Annalen*, 1934, **512**, 89) formed condensation

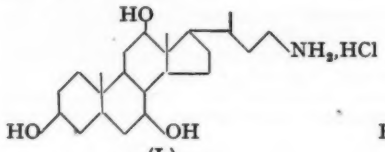
products of *p*-arsanilic acid with the 3-chlorocarboxyl derivatives of cholesterol and cholic acid. The compounds, however, exhibited no activity against *Spirillæ*.

Some derivatives of sulphanilamide with cholic acid were made by Haslewood (*Biochem. J.*, 1941, **35**, 1307). It was found (Barber, Dible, and Haslewood, *Biochem. J.*, 1943, **37**, VI) that the compound R·CO·NH·NH·SO_2–C$_6$H$_4$–NH_2 (R = cholyl) had considerable bacteriostatic activity against *Streptococcus hæmolyticus* and *Streptococcus pneumoniæ* but had no action on the coliform group of organisms.

Bile salts have a marked action in removing the ribonucleic acid and other constituents from the surface of certain Gram-positive micro-organisms (Henry and Stacey, *Nature*, 1943, 157, 671) so that it was deemed desirable to attempt the synthesis of some basic derivatives of sterols and bile acids in order to examine their bacteriostatic power. Moreover, the occurrence of steroid substances throughout the animal body suggested that this type of molecule might form a vehicle for the conveyance of groups such as amino-, amidino-, and guanidino-, known to have anti-bacterial power, to the most deeply seated tissues. Further, the possibility that some basic steroid derivatives might show anti-carcinogenic activity was envisaged.

23-Amino-3 : 7 : 12-trihydroxynorcholane and 23-amino-3 : 12-dihydroxynorcholane have been described by Caldwell (*J. Amer. Chem. Soc.*, 1938, **60**, 991; 1939, **61**, 3584) and the cyano-group was introduced into the sterol nucleus by Butenandt (*Ber.*, 1938, **71**, 1487; 1939, **72**, 182). 7-Aminocholestane was prepared by Eckhardt (*Ber.*, 1938, **71**, 461) and the preparation of new amino-derivatives of cholestane was carried out side by side with the present work (see Barnett, Ryman, and Smith, this vol., pp. 524, 528).

The present communication deals with some basic derivatives of cholane and norcholane. These may be conveniently divided into two groups, those with the basic group in the side chain and those with basic groups in the nucleus.



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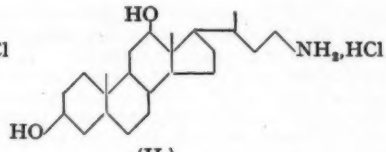

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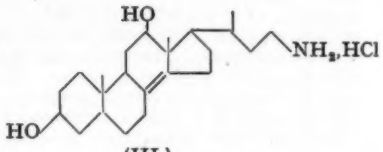

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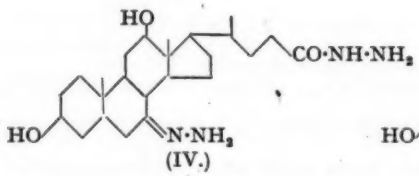

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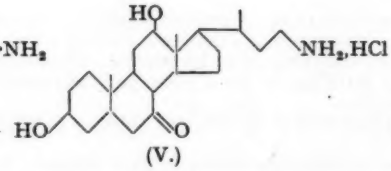

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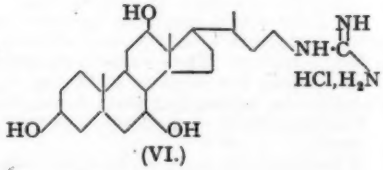

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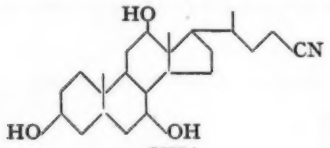

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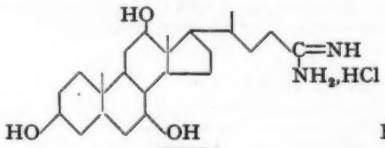

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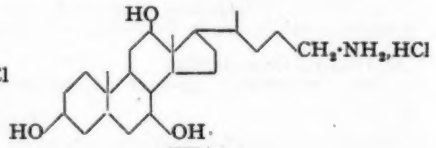

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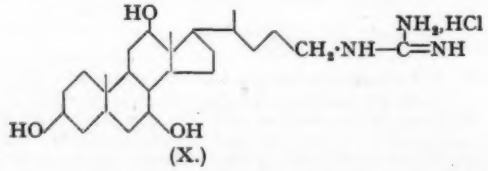

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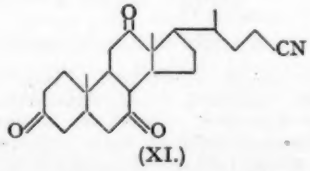


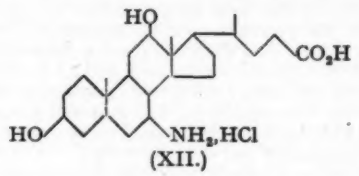
(XI.)

Of the first group the hydrochlorides of 23-amino-3 : 7 : 12-trihydroxynorcholane (I) and 23-amino-3 : 12-dihydroxynorcholane (II) were prepared in crystalline form by the method of Caldwell (*loc. cit.*). *23-Amino-3 : 12-dihydroxy-Δ⁸-norcholene* (III) was made by a similar method involving the decomposition, *via* the corresponding azide, of *3 : 12-dihydroxy-Δ⁸-cholenylhydrazine*. *23-Amino-3 : 12-dihydroxy-7-ketonorcholane hydrochloride* (V) was also prepared by a similar series of reactions. Ethyl 3 : 12-dihydroxy-7-ketocholanate (Haslewood, *Biochem. J.*, 1944, **38**, 108) on treatment with hydrazine in aqueous alcohol afforded *3 : 12-dihydroxy-7-ketocholanylhydrazine 7-hydrazone* (IV); this was converted, by the action of nitrous acid, into the azide which was subsequently decomposed by glacial acetic acid to give 23-amino-3 : 12-dihydroxy-7-ketonorcholane, isolated as the *hydrochloride* (V). *23-Guanido-3 : 7 : 12-trihydroxynorcholane hydrochloride* (VI) was produced by the interaction of cyanamide and (I) in absolute alcohol at 130°.

The synthesis of *3 : 7 : 12-trihydroxy-23-cyanonorcholane* (VII), which was used for the preparation of *23-amidino-3 : 7 : 12-trihydroxynorcholane hydrochloride* (VIII) and *24-amino-3 : 7 : 12-trihydroxycholane hydrochloride* (IX), was achieved in the following way. Methyl cholate was smoothly converted by alcoholic ammonia into cholylamide which afforded triformylcholylamide on being heated with formic acid. This product

was identical with a sample prepared by the method of Cortese and Bauman (*J. Amer. Chem. Soc.*, 1935, **57**, 1393) though our method of synthesis appeared to provide an easier route. Dehydration of triformylcholylamide by thionyl chloride gave 3 : 7 : 12-*triformyl*-23-*cyanonorcholane*. Ready removal of the formyl groups from this was effected by treatment with dilute sodium hydroxide and there resulted 3 : 7 : 12-trihydroxy-23-cyanonorcholane (VII). Alkaline hydrolysis of (VII) gave cholic acid, so that the treatment with thionyl chloride had affected the amide group only. Reduction of (VII) with sodium and amyl alcohol gave 24-amino-3 : 7 : 12-trihydroxycholane hydrochloride and the same product was obtained from (VII), though in comparatively poor yield, by catalytic hydrogenation. Cholylamidine hydrochloride was prepared by the method of Pinner (" Die Imido Äther ") though without the intermediate isolation of the imino ether. 24-*Guanido*-3 : 7 : 12-*trihydroxycholane hydrochloride* (X) was obtained by treatment of (IX) with cyanamide.

Two compounds containing basic groups in the nucleus were prepared. These were 7-*amino*-3 : 12-*dihydroxycholanic acid hydrochloride* (XII) and a *diamino-keto-acid*, presumably 3 : 7-diamino-12-ketocholanic acid dihydrochloride (XIII). No attempt was made to separate the α- and β-forms of nuclear substituted derivatives.



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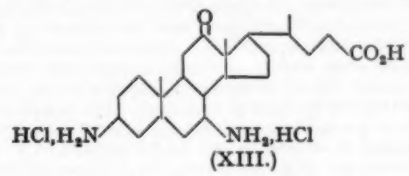

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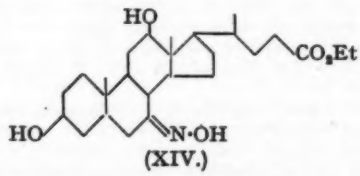

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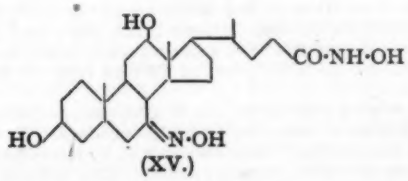

(XV.)

Ethyl 3 : 12-dihydroxy-7-ketocholanate on treatment with hydroxylamine at 80° for 3 hours gave the corresponding *oxime* (XIV). Reaction at higher temperatures and for a longer period resulted in the formation of the *oxime hydroxamic acid* (XV). Reduction of the oxime (XIV) by the method of Eckhardt (*loc. cit.*) gave 7-amino-3 : 12-dihydroxycholanic acid, isolated either as the crystalline hydrochloride above or as the 7-*benzamido*-derivative. The diamino-keto-acid was prepared by reduction, using sodium in amyl alcohol, of the trioxime derived from dehydrocholic acid followed by the removal of the residual oxime residue presumably attached to C_{12}. The product was isolated as the dihydrochloride (XIII).

No success was achieved in the introduction of cyano-groups into the nucleus. Pirronne (*Gazzetta*, 1932, **62**, 1101) reported the preparation of dicyanocholesterol by the action of anhydrous hydrogen cyanide upon cholesterol dibromide. We were unable to repeat this work and similar treatment of various halogen derivatives of steroids failed to give products containing nitrogen. The preparation of a cyanohydrin from dehydrocholic acid was attempted. While there was some indication that such a compound was formed efforts to isolate it failed and attempted dehydration of the crude material by the method of Butenandt (*Ber., loc. cit.*) did not give the required cyanide.

An attempt was made to prepare 3 : 7 : 24-triamino-12-ketocholane trihydrochloride. Oxidation of (VII) by the method of Hammarsten (*Ber.*, 1881, **14**, 71) gave 3 : 7 : 12-*triketo*-23-*cyanocholane* (XI) from which a *trioxime* was obtained. Reduction of the trioxime gave a product containing the triamine, but an acidic compound, probably (XIII), was also present.

Nuclear amines were found to have little or no *in vitro* bacteriostatic activity against *Staph. aureus* and *Lactobacillus helveticus*. Of the basic cholane and norcholane derivatives 23-guanido-3 : 7 : 12-trihydroxynorcholane had as shown below the highest *in vitro* bacteriostatic activity. This compound inhibited the growth of Gram-positive organisms at dilutions up to 1 : 64,000 but was only weakly bacteriostatic (1 : 4,000) for the Gram-negative bacillus, *Lactis ærogenes*.

The bacteriostatic activities of the basic derivatives were determined against *Staph. aureus*, *Lactobacillus helveticus*, and *B. lactis ærogenes* by the serial dilution method in glucose–peptone broth medium.

Hydrochlorides of :	Limiting dilution inhibiting growth after 24 hours at 37°. *Staph. aureus.*	*L. helveticus.*	*B. lactis ærogenes.*
23-Amino-3 : 7 : 12-trihydroxynorcholane	1 : 16,000	1 : 16,000	1 : 2000
23-Amino-3 : 12-dihydroxynorcholane	inactive	1 : 8,000	inactive
23-Amino-3 : 12-dihydroxy-7-ketonorcholane	inactive	1 : 1,000	inactive
Cholylamidine	1 : 2,000	1 : 2,000	1 : 1000
23-Guanido-3 : 7 : 12-trihydroxynorcholane	1 : 64,000	1 : 64,000	1 : 4000
24-Amino-3 : 7 : 12-trihydroxycholane	1 : 8,000	1 : 8,000	1 : 2000
23-Amino-3 : 12-dihydroxy-Δ^8-norcholene	1 : 8,000	1 : 8,000	1 : 1000
3 : 7-Diamino-12-ketocholanic acid	inactive	inactive	inactive
7-Amino-3 : 12-dihydroxycholanic acid	inactive	inactive	inactive

Experimental.

23-*Amino*-3 : 7 : 12-*trihydroxynorcholane Hydrochloride* (*Cholamine Hydrochloride*).—This compound was prepared by the method of Caldwell (1938, *loc. cit.*) and had $[\alpha]_D^{21°}$ + 32·7° in water (*c*, 0·6), m. p. 315° (decomp.) (Found: Cl, 7·5. Calc. for $C_{23}H_{42}O_3NCl$: Cl, 8·5%). "Cholamine hydrochloride" was obtained in crystalline form by the addition of a few drops of 5N-hydrochloric acid to a solution of the free base in acetone. The needle-like crystals obtained showed $[\alpha]_D^{18°}$ + 32·2° in water (*c*, 1·0) (Found: N, 4·0. Calc. for $C_{23}H_{42}O_3NCl$: N, 3·4%).

23-*Amino*-3 : 12-*dihydroxynorcholane*.—This compound was obtained by the method of Caldwell (1939, *loc. cit.*). The crude base had m. p. 127—129°, $[\alpha]_D^{18°}$ + 45·9° in alcohol (*c*, 1·8). The addition of ethereal hydrogen chloride to a solution of the dry base in absolute alcohol resulted in the separation of the *hydrochloride*, which was collected at the pump and washed with ether. On recrystallisation from aqueous acetone small prisms were obtained having m. p. 283° and $[\alpha]_D^{18°}$ + 52·9° in alcohol (*c*, 0·3) (Found: N, 4·0. $C_{23}H_{42}O_3NCl$ requires N, 3·5%).

Apocholylhydrazine.—Methyl apocholate (4 g.) (Boedecker, *Ber.*, 1920, **53**, 1852) was boiled under reflux for 10 hours with ethyl alcohol (14 c.c.) and an aqueous solution of hydrazine hydrate (8 c.c. of 50%). The solution was then concentrated under reduced pressure and finally evaporated to dryness in a vacuum over concentrated sulphuric acid. Recrystallisation of the residue from ethyl acetate gave white needles (2·9 g.) of *apocholylhydrazine*, m. p. 191—192°, $[\alpha]_D^{21°}$ + 35·6° in alcohol (*c*, 1·5) (Found: N, 6·9. $C_{24}H_{40}O_3N_2$ requires N, 6·9%).

23-*Amino*-3 : 12-*dihydroxy*-Δ^8-*norcholene*.—Sodium nitrite solution (0·5N) was slowly added to apocholylhydrazine (2·5 g.), dissolved in hydrochloric acid (400 c.c., 0·1N) at 0°, until the presence of a slight excess of nitrous acid was detected with starch–iodide paper. The mixture was kept at 0° for ½ hour and then the precipitated azide was collected at the pump, washed with water, and transferred while still moist into glacial acetic acid (30 c.c.). The mixture was heated at 100° for about 1 hour when the evolution of gas ceased, and was then cooled to 0° and made alkaline to litmus by the addition of sodium hydroxide solution. The precipitated *amine* was collected in a sintered glass funnel, washed with water, dried in a vacuum over phosphorus pentoxide and sodium hydroxide, and recrystallised from toluene. Crystals were obtained having m. p. 97—100° (Found: N, 4·3. $C_{23}H_{39}O_2N$ requires N, 3·9%).

23-*Amino*-3 : 12-*dihydroxy*-Δ^8-*norcholene Hydrochloride* ("*Apocholamine Hydrochloride*") (III).—Dry hydrogen chloride was led into a solution of the crude amine in chloroform until the precipitation of the hydrochloride was complete. The supernatant liquid was decanted and the residual gum was triturated with acetone until it became solid. The *hydrochloride* was recrystallised from aqueous acetone containing a few drops of hydrochloric acid. Colourless needles were obtained, m. p. >290°, which showed $[\alpha]_D^{18°}$ + 39·3° in alcohol (*c*, 2·0) (Found: N, 3·7. $C_{23}H_{40}O_2NCl$ requires N, 3·5%).

Hydrazone of **3 : 12-*Dihydroxy*-7-*ketocholanylhydrazine*** (IV).—Ethyl 3 : 12-dihydroxy-7-ketocholanate (10 g.) in ethyl alcohol (50 c.c.) was boiled under reflux for 30 hours with aqueous hydrazine hydrate (10 c.c. of 50%) and the solution was concentrated to about 20 c.c. under reduced pressure and finally evaporated to dryness in a vacuum desiccator over concentrated sulphuric acid. The residue (5·8 g.) was finely powdered, dried in a vacuum at 100°, and recrystallised from ethyl acetate to give colourless needles of the *hydrazone*, $[\alpha]_D^{18°}$ − 92·3° in alcohol (*c*, 1·3), m. p. >300° (Found: N, 12·9. $C_{24}H_{42}O_3N_4$ requires N, 12·9%).

23-*Amino*-3 : 12-*dihydroxy*-7-*ketonorcholane* (V).—3 : 12-Dihydroxy-7-ketocholanylhydrazine hydrazone (3·6 g.) was treated with sodium nitrite in acid solution as described for the preparation of apocholamine (see above) except that the decomposition of the azide was carried out at 60—70°. The free base finally obtained was dried in a vacuum over phosphorus pentoxide and sodium hydroxide and was then exhaustively extracted with boiling toluene. The extract was dried by slow distillation of the toluene during 4 hours, filtered, and allowed to cool. The amine separated in small needles (m. p. 123—127°) which were washed by decantation with toluene, dried in a vacuum, and dissolved in absolute ethyl alcohol. A stream of dry hydrogen chloride was led into the cooled alcoholic solution and then the amine hydrochloride was precipitated by the addition of dry ether. The solid was washed by decantation with ether, dried in a vacuum, and crystallised from aqueous acetone containing a little hydrochloric acid. The *product* (0·8 g.) formed small prisms, m. p. 263° (decomp.), $[\alpha]_D^{18°}$ ± 0° in alcohol (*c*, 0·43) (Found: Cl, 8·8; N, 3·4. $C_{23}H_{40}O_2NCl$ requires Cl, 8·6; N, 3·4%).

23-*Guanido*-3 : 7 : 12-*trihydroxynorcholane Hydrochloride* (VI).—A sample of the crystalline "cholamine hydrochloride" (1 g.) was heated with cyanamide (1 g.) in sodium-dry alcohol (25 c.c.) at 130° for 17 hours. The solution was filtered and concentrated to small bulk. Crystals of dicyanamide then separated; these were removed and the mother liquor was poured into dry acetone (200 c.c.) with stirring. The white solid *hydrochloride* (0·45 g.) which was precipitated was separated on the centrifuge and washed with acetone. It gave a positive Sakaguchi test and after recrystallisation from aqueous acetone showed $[\alpha]_D^{23°}$ + 41° in 50% aqueous alcohol (*c*, 0·5), m. p. 246° (Found: N, 9·1; Cl, 7·2. $C_{24}H_{44}O_3N_3Cl$ requires N, 9·3; Cl, 7·8%).

Cholylamide.—Methyl cholate (30 g.) was heated in the autoclave for 12 hours at 130° and 30 atmospheres' pressure with methyl alcohol (300 c.c.) which had been saturated at 0° with ammonia. The solution was evaporated to dryness and the residue recrystallised from 30% aqueous alcohol (charcoal). The crystals (21·7 g.; 75% of the theory) had m. p. 105° alone and in admixture with a specimen of cholylamide prepared by the method of Cortese and Baumann (*loc. cit.*).

Triformylcholylamide.—Cholylamide (6·7 g.) was heated at 55—60° with freshly distilled formic acid (75 c.c.) for 5 hours and then kept overnight. The excess of acid was removed under diminished pressure and the residue dissolved in acetone–benzene. The addition of light petroleum to the solution resulted in the separation of crystals of triformylcholylamide which, after a short time, were filtered off and washed with light petroleum. The crystals (3 g.) had m. p. 187° in agreement with Cortese and Baumann (*loc. cit.*). A further crop of crystals (1·2 g.) was obtained from the mother liquor.

Triformylcholyl Cyanide.—Triformylcholylamide (3 g.) was boiled under reflux for 3½ hours with thionyl chloride (50 c.c.) and then the thionyl chloride was removed under reduced pressure. The glass-like residue was taken up in acetone and the solution slowly poured into water with stirring. The solid which separated was filtered at the pump and washed with water. It was combined with the product from a second experiment in which the same amounts were used, and recrystallised from aqueous acetone to give crystals of *triformylcholyl cyanide* (3·5 g.), m. p. 188° depressed in admixture with triformylcholylamide (Found: N, 3·2. $C_{27}H_{39}O_6N$ requires N, 3·0%).

Cholyl Cyanide.—Triformylcholyl cyanide (3·54 g.) was dissolved in alcohol and sodium hydroxide solution (25 c.c., 1 N) was added. The solution was heated at 50—60° for 1 hour and was then diluted with water. Needle-like crystals immediately separated. These were filtered off, washed with water, and dried in a vacuum desiccator (2·3 g.), m. p. 216—218°. After recrystallisation from aqueous alcohol crystals of *cholyl cyanide* (VII), m. p. 218°, $[\alpha]_D^{18°}$ + 38·7° in alcohol (*c*, 0·9), were obtained (Found: C, 73·6; H, 10·2; N, 3·6. $C_{24}H_{39}O_3N$ requires C, 73·96; H, 10·1; N, 3·64%).

Hydrolysis of Cholyl Cyanide.—Cholyl cyanide (0·14 g.) was boiled under reflux for 9 hours with potassium hydroxide solution (1 c.c., 40%). The solution was cooled and acidified with dilute hydrochloric acid. A crystalline solid (0·12 g.)

separated which, after recrystallisation from ethyl alcohol, had m. p. 196° alone and in admixture with an authentic specimen of cholic acid.

Cholylamidine Hydrochloride (VIII).—Cholyl cyanide (2·3 g.) was dissolved in sodium-dry ethyl alcohol (45 c.c.) and sodium-dry ethyl alcohol (15 c.c.) saturated at 0° with dry hydrogen chloride was added. The solution was kept at 0° for 68 hours and then as much as possible of the excess hydrogen chloride was removed by means of a current of dry air. An alcoholic solution (75 c.c.) of ammonia (saturated at 0°) was then carefully added to the cooled solution and the mixture was kept overnight at 0°. The ammonium chloride which separated was filtered off and the filtrate evaporated to dryness. The residue was extracted with cold water (100 c.c.). The insoluble material was recrystallised from aqueous alcohol to give crystals (1·12 g.) of cholyl cyanide, m. p. and mixed m. p. 218°. Evaporation of the mother-liquor gave a residue which was recrystallised from alcohol, ether, and light petroleum. Clusters of needle-like crystals (0·194 g.) of *cholylamidine hydrochloride* separated, m. p. 295°, $[\alpha]_D^{18°}$ + 27° in water (*c*, 0·9) (Found : C, 65·3; H, 9·9; N, 6·2; Cl, 7·3. $C_{24}H_{43}O_2N_2Cl$ requires C, 65·0; H, 9·8; N, 6·3; Cl, 8·0%). The aqueous extract was evaporated to dryness and re-extracted with water (75 c.c.). The crystalline material (0·47 g.) which did not dissolve had m. p. 290° alone and in admixture with the cholylamidine hydrochloride previously isolated. A further quantity of (VIII) was obtained by salting out from the aqueous extract. It was freed from sodium chloride by extraction with alcohol. Evaporation of the extract gave a residue which was recrystallised from alcohol, ether, and light petroleum to give crystals (0·1 g.), m. p. 290°. Thus the total yield of cholylamidine hydrochloride was 0·76 g.

24-*Amino*-3 : 7 : 12-*trihydroxycholane Hydrochloride* (IX).—(*a*) Cholyl cyanide (1·75 g.) was dissolved in amyl alcohol (200 c.c.) and the solution was boiled under reflux during the gradual addition of sodium (20 g.) over 3½ hours. Towards the end of the reaction a further amount of amyl alcohol (50 c.c.) was added. The solution was cooled and diluted with water (300 c.c.). The alcoholic layer was separated, washed repeatedly with water, and evaporated to dryness under diminished pressure. The residue was digested overnight with dilute hydrochloric acid (470 c.c., 0·04N); a small amount of syrupy material did not dissolve. Addition of sodium hydroxide solution in excess to the aqueous extract brought about the separation of a white solid which was quickly filtered on a glass sintered funnel, washed with water, and dried in a vacuum over soda lime. Yield, 1·12 g. The free base (1·02 g.) was dissolved in dry chloroform and dry hydrogen chloride was led into the solution. The hydrochloride (0·62 g.) which separated was obtained as a white powder on trituration with ether. It was recrystallised from aqueous acetone to which a drop of very dilute hydrochloric acid was added when small needle-like crystals of 24-*amino*-3 : 7 : 12-*trihydroxycholane hydrochloride* were obtained, m. p. 267° (decomp.), $[\alpha]_D^{21°}$ + 34° in alcohol (*c*, 0·9) (Found : N, 3·9; Cl, 8·2. $C_{24}H_{44}O_3NCl$ requires N, 3·3; Cl, 8·3%).

(*b*) Cholyl cyanide (2·5 g.), purified by sublimation in a vacuum, was ground to a fine powder and hydrogenated in ether (600 c.c.) in the presence of Raney nickel at 115—120° and 160 atmospheres for 3 hours with continuous stirring. After allowing to cool overnight the mixture was evaporated in nitrogen to give a syrupy product which was alkaline in reaction. It was dissolved in alcohol and a drop of concentrated hydrochloric acid was added and then acetone and light petroleum until a faint turbidity developed. Crystals (0·13 g.) quickly separated and were filtered off, m. p. 263° (decomp.). Evaporation of the mother liquor at 40° (bath temp.) under reduced pressure gave a crystalline residue which was extracted with cold water. Recrystallisation of the insoluble material from aqueous alcohol gave crystals (1·52 g.) of cholyl cyanide, m. p. and mixed m. p. 215°. The aqueous extract was neutralised (phenolphthalein) and evaporated to dryness to give a residue which was extracted first with acetone to remove unchanged cholyl cyanide and then with ethyl alcohol to remove sodium chloride. Evaporation of the filtered extract gave a residue consisting of (IX) which was recrystallised from ethyl alcohol and acetone containing a little hydrochloric acid. Crystals (0·1 g.) were obtained, m. p. 267° (decomp.), $[\alpha]_D^{18°}$ + 30° in water (*c*, 1·0). The total yield of (IX) was 0·23 g. (9%).

24-*Guanido*-3 : 7 : 12-*trihydroxycholane Hydrochloride* (X).—24-Amino-3 : 7 : 12-trihydroxycholane hydrochloride (0·3 g.) was heated with cyanamide (0·3 g.) in sodium-dry alcohol (40 c.c.) in a sealed tube at 130° for 17 hours. The solution, which gave a positive Sakaguchi test, was concentrated to small bulk and a solid (0·1 g.) precipitated by the addition of acetone. This was dissolved in a few drops of dilute hydrochloric acid and acetone was added. The product (27 mg.) was separated in the centrifuge, washed with acetone, and dried in a vacuum. It had $[\alpha]_D^{14°}$ + 23° in alcohol (*c*, 0·9) (Found : N, 9·0. $C_{25}H_{46}ONCl$ requires N, 8·9%).

Dehydrocholyl Cyanide (3 : 7 : 12-*Triketo*-23-*cyanonorcholane*) (XI).—Cholyl cyanide (2·1 g.) was dissolved in glacial acetic acid (5 c.c.) and a 10% solution of chromic acid in glacial acetic acid (35 c.c.) was added in small portions. The temperature was not allowed to rise above 40°. When all the oxidising mixture had been added the solution was allowed to stand for 15 minutes and was then diluted with water (500 c.c.). The insoluble product was filtered off and washed with water. Recrystallisation from ethyl alcohol afforded crystals (1·15 g.) of *dehydrocholyl cyanide*, m. p. 242° (Found : C, 75·5; H, 8·6; N, 3·85. $C_{24}H_{33}O_3N$ requires C, 75·2; H, 8·7; N, 3·65%).

Trioxime of Dehydrocholyl Cyanide.—Dehydrocholyl cyanide (1·15 g.) was dissolved in ethyl alcohol (105 c.c.) and boiled under reflux with hydroxylamine hydrochloride (0·58 g. in 1·25 c.c. of water) and sodium acetate (1·25 g. in 2·5 c.c. water) for 10 hours. No separation of an oxime occurred and after standing overnight the clear solution was poured into water. The white solid which separated was filtered off, washed with water, and recrystallised from aqueous alcohol, m. p. 225° (decomp.) (Found : N, 13·1. $C_{24}H_{36}O_3N_4$ requires N, 13·3%).

Oxime of Ethyl 3 : 12-*Dihydroxy*-7-*ketocholanate.*—Hydroxylamine hydrochloride (4·8 g.), dissolved in the minimum amount of water, was mixed with a solution of sodium hydroxide (12 c.c., 5N) and alcohol (50 c.c.) was added. The precipitate of sodium chloride was filtered off and ethyl 3 : 12-dihydroxy-7-ketocholanate (10 g.), dissolved in absolute alcohol (50 c.c.), was added to the filtrate and the solution was heated at 70—80° under reflux for 4 hours. Subsequent removal of the solvent under reduced pressure afforded a residue which was extracted with ether. The extract was dried ($MgSO_4$), filtered, and evaporated to dryness to give the *oxime* (XIV) (6·2 g.). On recrystallisation from methyl alcohol large rectangular plates were obtained, m. p. 93—94°, $[\alpha]_D^{14°}$ − 44·3° in alcohol (*c*, 5·9) (Found : N, 3·1. $C_{26}H_{43}O_4N$ requires N, 3·1%). A further quantity of oxime (1·2 g.), m. p. 91°, was obtained from the mother liquors.

Oxime of the Hydroxamic Acid (XV).—Ethyl 3 : 12-dihydroxy-7-ketocholanate (1·2 g.), hydroxylamine hydrochloride (0·58 g.), and sodium hydroxide (7·5 c.c., 1N) in ethyl alcohol (10 c.c.) were boiled under reflux for 5 hours. The solvents were distilled off under diminished pressure and the residue extracted three times with methyl alcohol (20 c.c.). The combined extracts were concentrated to half volume under reduced pressure and kept for 16 hours. The crystals which separated were collected, washed with methyl alcohol, and recrystallised from the same solvent. Large plates (0·5 g.) were obtained, m. p. 214—215° (decomp.), $[\alpha]_D^{18°}$ − 51·4° in alcohol (*c*, 1·9) (Found : C, 66·1; H, 8·95; N, 6·6. $C_{24}H_{40}O_5N_2$ requires C, 66·1; H, 9·2; N, 6·4%).

The *oxime* was acid to litmus, and dissolved in dilute sodium hydroxide and was precipitated on acidification of the alkaline solution. It was readily soluble in methyl and ethyl alcohols, soluble in ethyl acetate, sparingly soluble in ether, chloroform, and benzene, and insoluble in water.

7-*Amino*-3 : 12-*dihydroxycholanic Acid.*—Sodium (30 g.) was added in small quantities over a period of 4 hours to a solution of (XIV) (10 g.) in amyl alcohol (500 c.c.) at 100°. An additional 50 c.c. of amyl alcohol were required to dissolve the last traces of sodium. The cooled solution was made neutral to litmus by the addition of sulphuric acid

(5N) and was kept for 14 hours. The sodium sulphate which separated was filtered off and washed with ethyl alcohol. The filtrate and washings were evaporated to dryness under reduced pressure and the residue, dried in a vacuum at 100°, was exhaustively extracted with absolute alcohol. Evaporation of the extract gave crude sodium 7-amino-3 : 12-dihydroxycholanate (9·4 g.) as an amorphous, water-soluble yellow solid.

Hydrochloride of 7-Amino-3 : 12-dihydroxycholanic Acid (XII).—A solution of crude sodium 7-amino-3 : 12-dihydroxycholanate (3 g.) in absolute alcohol (15 c.c.) was treated with a slow stream of dry hydrogen chloride until no further separation of sodium chloride occurred. The solution was filtered and the residue washed with ethyl alcohol. The filtrate and washings were concentrated under diminished pressure, and the amine hydrochloride precipitated by the addition of dry ether, washed by decantation with anhydrous ether, and dried in a vacuum. The white solid (2·0 g.) crystallised from 50% aqueous ethyl alcohol after long standing, forming large colourless prisms (0·5 g.), m. p. 265—267° (decomp.) (Found: N, 3·2; Cl, 7·7. $C_{24}H_{42}O_4NCl$ requires N, 3·2; Cl, 8·0%). The *compound* was readily soluble in water, soluble in ethyl and methyl alcohols, insoluble in other organic solvents.

7-Benzamido-3 : 12-dihydroxycholanic Acid.—Sodium 7-amino-3 : 12-dihydroxycholanate (0·9 g.) in water (25 c.c.) containing sodium hydroxide (0·4 g.) was treated with benzoyl chloride (0·36 c.c.) added dropwise with shaking over a period of 5 minutes. The solution was kept at room temperature for a further 15 minutes with frequent agitation and was then warmed to 50—60° for a short time. The cooled solution was acidified with dilute hydrochloric acid and the precipitate filtered off after 16 hours and washed with water until free from acid and then with ether. The residue was dissolved in methyl alcohol and the filtered solution evaporated under reduced pressure to give a solid which crystallised on trituration with benzene. Recrystallisation from a large volume of benzene afforded the *benzoyl* derivative of (XII) as colourless plates (0·4 g.), m. p. 185°, $[\alpha]_D^{16°}$ + 39·4° in alcohol (*c*, 1·3) (Found: N, 2·65. $C_{31}H_{45}O_5N$ requires N, 2·7%).

Reduction of 3 : 7 : 12-Trioximinocholanic Acid.—The trioxime (3·1 g.), derived from dehydrocholic acid prepared according to the method of Schenck and Kirchhof (*Z. physiol. Chem.*, 1929, **181**, 193), was boiled under reflux with amyl alcohol (750 c.c.) for 5½ hours during the gradual addition of sodium (40 g.). The cooled solution was poured into water and the alcoholic layer was separated and repeatedly washed with water and then evaporated to dryness under reduced pressure. The residue was dissolved in the minimum amount of water and hydrochloric acid was added until the solution was just acid to litmus. The volume was then made up to 100 c.c. and the acidity adjusted to 1N, and the solution was boiled for 1 hour to ensure the elimination of the oxime group from C_{12}. The solution was filtered, diluted with water (200 c.c.), and evaporated to dryness under reduced pressure at 40° to give a residue which was extracted with alcohol. Removal of solvent from the filtered extract gave a resinous product (1·49 g.) which was purified by extracting with cold water and filtering from some insoluble material (0·27 g.). Evaporation of the filtrate gave a colourless residue which was dissolved in ethyl alcohol; ether was then added to the clear solution. A white precipitate was produced and was separated on the centrifuge, washed with ether, and dried in the vacuum desiccator. This *product* (XIII) (1·06 g.) was readily soluble in water and showed $[\alpha]_D^{16°}$ + 42° in water (*c*, 0·7). A 2% solution had pH 3·1 (Found: N, 5·3; Cl, 14·84. $C_{24}H_{43}O_3N_3Cl_3$ requires N, 5·9; Cl, 14·88%). The aqueous washings from the amyl alcohol were examined and a further amount (0·85 g.) of the dihydrochloride of the diamino-acid was obtained.

Reduction of Trioximinocholyl Cyanide.—The trioxime (0·95 g.), derived from 3 : 7 : 12-triketo-23-cyanonorcholane prepared as described above, was boiled under reflux with amyl alcohol (250 c.c.) for 3 hours during the gradual addition of sodium (15 g.). The product was isolated as described in the previous experiment. A white powder (0·3 g.) was obtained which was probably a mixture of the dihydrochloride of the diamino-acid and the trihydrochloride of the triamino-monoketo-derivative of cholane, since it dissolved in water to give an acid solution and contained 17·6% Cl (Calc. for $C_{24}H_{43}O_3N_3Cl_2$: Cl, 14·88%. Calc. for $C_{24}H_{47}ON_3Cl_3$: Cl, 21·0%).

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137. *The Light Absorption and Resonance Energies of Some Heterocyclic Molecules.*

By Allan Maccoll.

In view of the pronounced red shift of the long wave-length electronic absorption band of the cyclic molecules $[CH]_nN_{6-n}$ as *n* decreases, the quantum mechanics of these molecules has been investigated to the Förster approximation. If it is assumed that the C–C, C–N, N–N exchange integrals decrease in that order, the observed shifts can be accounted for. The resonance energies of these compounds have also been determined, together with the zeroth order wave functions in those cases in which the two Kekulé forms are non-equivalent.

The observation of the absorption spectra of a number of members of the class $[CH]_nN_{6-n}$ ($n \leqslant 6$), in which the CH groups of the benzene molecule are progressively replaced by the isoelectronic nitrogen atom, has made possible a comparison with quantum-mechanical prediction. The compounds investigated in the gas phase are benzene (Nordheim, Sklar, and Teller, *J. Chem. Physics*, 1939, **7**, 207), pyridine (Sponer, *Rev. Mod. Physics*, 1944, **16**, 244), pyrimidine (Uber, *J. Chem. Physics*, 1941, **9**, 777), and *s*-tetrazine (Koenigsberger and Vogt, *Physikal. Z.*, 1913, **14**, 1269). In solution, 2 : 6-diphenylpyrazine (Tutin and Caton, *J.*, 1910, **97**, 2524) and pyridazine (Evans and Wiselogle, *J. Amer. Chem. Soc.*, 1945, **67**, 79) have been studied. In the case of benzene and pyridine, the long wave-length ultra-violet absorption bands have been analysed, and the respective origins are at 2600 and 2900 A. Pyridine is of interest in that there is a relatively large shift in wave-length (*ca.* 300 A.) on changing from solution in hexane to the gas phase. The data for pyrimidine and *s*-tetrazine have not been analysed, and the absorption maxima are estimated to lie at 3100 and 5200 A., respectively. For 2 : 6-diphenylpyrazine and pyridazine the published absorption curves would suggest that the absorption maxima lie at 3160 and 3380 A. Since the last two substances have been measured in solution, the data are not strictly comparable with those for the former compounds, which were investigated in the gas phase. From the experimental results it may be concluded that the substitution of CH groups in

a benzene ring by nitrogen atoms leads to a shift of the long wave-length electronic band towards the red. The effect is most marked when the nitrogen atoms occupy adjacent positions.

The foregoing data suggested an application of the valence-bond method to the series of molecules under consideration. This method was adapted by Pauling (*J. Chem. Physics*, 1933, **1**, 280) for calculating the ground states of complex molecules, and Sklar (*ibid.*, 1937, **5**, 669) was the first to utilise it in connection with the excited states. These calculations yield both the resonance energy and the wave-lengths of maximum absorption of the electronic bands. The valence-bond method assumes that in a conjugated system the s, p_x, p_y electrons of each atom taking part in the conjugation hybridise to form a trigonal framework, while the p_z electrons are free to couple in a number of different ways. This gives rise to spin degeneracy, and the required energy levels are the roots of the quantum-mechanical secular equation. For the molecules in question, this can be set up in terms of the five canonical structures and thus will be of the fifth degree. However, as in the case of benzene, group theoretical methods lead to a simplification of the secular equation in those cases where the molecule possesses elements of symmetry other than the plane of the ring. As distinct from benzene, however, three different types of exchange integrals will occur: the C–C integral α, the C–N integral β, and the N–N integral γ, if the usual assumptions of the valence-bond method are made, namely, the neglect of ionic structures and exchange integrals between non-adjacent atoms. Hence, the resonance energy and light absorption of these molecules can be calculated in terms of three empirically determined constants, α, β, γ. Rather than solve the complete secular equation at this stage, recourse will be had to the method used by Förster (*Z. physikal. Chem.*, 1938, **41**, *B*, 287) in treating a series of polycyclic aromatic hydrocarbons. In this treatment, which is justified by the agreement with experiment, the approximation of only considering Kekulé-type (unexcited) structures was introduced. For the molecules under consideration, the secular equation reduces to a quadratic, which will in turn reduce to two linear factors when the two Kekulé structures are equivalent. The equations for the energy levels resulting from this treatment are given in the Appendix. The difference between the energy of the ground state and its value if only one Kekulé structure is considered is the resonance energy, while the energy difference between the two calculated states corresponds to the long wave-length electronic absorption band.

The constants used in the calculation are: α, 1·97, β, 1·38, and γ, 0·20 v.e. The energy difference for pyridazine and *s*-tetrazine does not depend very greatly upon γ and so its value cannot be considered to be very accurate. By using these values, the results shown in the table are obtained. The agreement between the observed and calculated absorption maxima is good in view of the approximations involved. The only data with which the calculated resonance energies can be compared are for benzene and pyridine. Wheland ("The Theory of Resonance," Wiley, New York, 1944) gives the value 41 Kcals. for benzene and 43 and 37 Kcals. for pyridine. If the latter value for pyridine is accepted, and it would appear reasonable to do so in view of the hygroscopic nature of pyridine, the agreement is satisfactory.

Calculated and observed wave-lengths of the first absorption bands, and the calculated resonance energies of some heterocyclic molecules.

Molecule.	Wave-length, A. Calc.	Obs.	Resonance energy (Kcals.).	Molecule.	Wave-length, A. Calc.	Obs.	Resonance energy (Kcals.).
Benzene	2600	2600	41	Pyridine	2900	2900	37
	Diazines.				Triazines.		
Pyrimidine	3240	3100	33	*s*-Triazine	3700	—	29
Pyrazine	3240	3160 [a]	33	*vic.*-Triazine	4330	—	25
Pyridazine	3360	3380	22 [b]	*as*-Triazine	3830	—	18 [c]
	Tetrazines.						
s-Tetrazine	5200	5200	20	Pentazine	8650	—	12
as-Tetrazine	5200	—	20				
vic.-Tetrazine	5300	—	10 [c]				

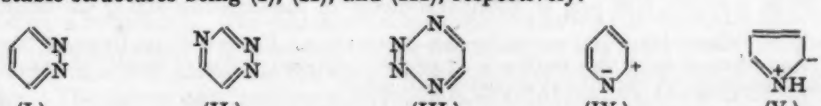
a. This value is for 2 : 6-diphenylpyrazine. *b*. Relative to the structure containing =N—N=. *c*. Relative to the structure containing =CH—CH=.

Evans and Wiselogle (*loc. cit.*) have pointed out the non-equivalence of the Kekulé structures for pyridazine. The same is true of *as*-triazine and *vic.*-tetrazine. It is of interest to calculate the relative importance of the two structures in these cases. The zeroth order (un-normalised) wave functions are:

Pyridazine $\psi = \psi_A + 1{\cdot}39\,\psi_B$ *vic.*-Tetrazine $\psi = \psi_A + 1{\cdot}72\,\psi_B$

as-Triazine $\psi = \psi_A + 1{\cdot}47\,\psi_B$

the three more stable structures being (I), (II), and (III), respectively.

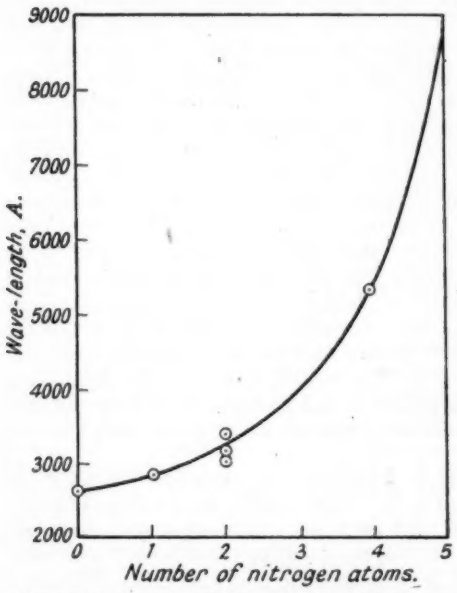


(I.) (II.) (III.) (IV.) (V.)

Bowen (*Ann. Reports*, 1943, **40**, 25) has commented upon the way in which N can replace CH in a compound with little effect upon its absorption spectrum. He quotes the case of anthracene and acridine, which

have very similar absorption spectra. However, the present calculations would suggest that the similarity in spectra is due rather to the buffering effect of the two fused benzene rings. The effect of the successive replacement of CH groups by nitrogen atoms in a benzene ring is shown in the figure, where the mean wave-length of the first absorption band of the molecules $[CH]_nN_{6-n}$ is plotted against the number of nitrogen atoms.

The neglect of ionic structures in the quantum-mechanical calculation must be more serious in the case of molecules involving C–N bonds than in the case of benzene. Because of the electronegativity of nitrogen, structure (IV), placing a negative charge on a nitrogen atom, would be stabilised. However, as Sklar (*loc. cit.*) has pointed out, ionic structures are highly excited and would be expected only to contribute appreciably to the higher energy states of the molecule. The case of 1 : 3-*cyclo*pentadiene and pyrrole is of interest in this connection. The resonance energy of pyrrole is 24 Kcals., while that of *cyclo*pentadiene is only 3 Kcals. (Wheland, *loc. cit.*). The differences lies in the fact that the nitrogen atom in pyrrole has a lone pair of electrons which can give rise to ionic structures like (V), whereas this possibility is absent in *cyclo*pentadiene. This is presumably responsible for a shift in the wave-length of maximum absorption from 2300 A. for *cyclo*pentadiene to 1800 A. for pyrrole (Price and Walsh, *Proc. Roy. Soc.*, 1941—1942, **179**, *A*, 201). That the ionic structures play a large part in pyrrole is also shown by the high intensity of absorption as compared with pyridine. Whereas in pyrrole the adverse charge distribution is outweighed by the formation of a double bond, in pyridine a desirable charge distribution has to be weighed against the decrease in stability due to the loss of a bond. The evidence is thus not inconsistent with the ground and first states of the pyridine molecule being mainly of a covalent character.



Absorption maxima of the molecules $[CH]_nN_{6-n}$. *The smooth curve passes through the calculated points, the experimental points being shown in circles.*

Calculations are proceeding with zeroth order wave functions including the five canonical structures. Preliminary results lead to the conclusion that pyridine on controlled reduction should form 1 : 4-dihydropyridine, while reduction of quinoline should first occur in the ring containing the nitrogen atom, in agreement with experiment. The use of the full canonical set gives rise to a differentiation of the energy levels of pyrimidine and pyrazine, which are equivalent when only the Kekulé-type structures are considered. It is also hoped to extend the treatment now described to other heterocyclic compounds.

Appendix.

The Solution of the Secular Equations.—(a) *The secular equation reduces to two linear factors :*

$$x = 0$$
$$x = -0{\cdot}8(p + q + r).$$

Molecule.	*p*.	*q*.	*r*.	Molecule.	*p*.	*q*.	*r*.
Benzene	1	1	1	*vic*.-Triazine	1	a	b
Pyridine	1	1	a	*s*-Tetrazine } *as*-Tetrazine }	a	a	b
Pyrimidine } Pyrazine }	a	a	1	Pentazine	b	b	a
s-Triazine	a	a	a				

(b) *The secular equation is quadratic :*

(i) Pyridazine.

$$15x^2 + (18 + 12a + 6b)x + [6 - 4(a - b)](8a - 2b) - (3 + 2a + b)^2 = 0$$

(ii) *as*-Triazine.

$$15x^2 + (6 + 24a + 6b)x + (4 - 2a + 4b)(-2 + 10a - 2b) - (1 + 4a + b)^2 = 0$$

(iii) *vic*.-Tetrazine.

$$15x^2 + (6 + 12a + 18b)x + [6b - 4(a - 1)](8a - 2) - (1 + 2a + 3b)^2 = 0$$

where $x = (Q - W)/\alpha$, $a = \beta/\alpha$, $b = \gamma/\alpha$, W being the energy of the molecule and Q the Coulomb integral.

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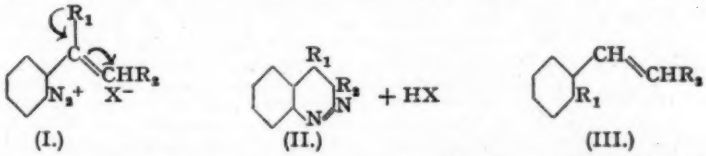
138. *Cinnolines. Part VII. Further Observations on the Widman–Stoermer Reaction.*

By J. C. E. Simpson.

Production of 4-aryl-3-alkyl-(or aryl)-cinnolines from appropriate diazotised *o*-aminoarylethylenes is independent of the steric configuration of the latter. Formation of cinnolines from (III; $R_1 = NH_2$; R_2 = α-pyridyl or α-quinolyl) was not observed. These facts support the ionic mechanism suggested (*J.*, 1945, 520) for the cinnoline synthesis.

Parts II and IV of this series (Simpson, *J.*, 1943, 447; Schofield and Simpson, *J.*, 1945, 520) have dealt with the factual and theoretical aspects of the Widman–Stoermer reaction, which is a general method for the synthesis of 4-aryl-, 4-aryl-3-alkyl-, 4-aryl-3-aralkyl-, and 3 : 4-diaryl-cinnolines. In Part IV this reaction (I ⟶ II) was represented as proceeding *via* a polarised form of a diazotised *o*-aminoarylethylene containing a suitable α-substituent, *i.e.*, one which reinforces the ethylenic polarisation depicted in (I) (R_1 = OH or aryl), and it was pointed out that the rapid formation of 3 : 4-diphenylcinnoline from each of the two possible geometrical forms



(I.) (II.) (III.)

of the aminoethylene supported the suggested mechanism to the extent that it indicated that the cyclisation must be more or less ionic in character. It has now been found that the production of other 3-substituted 4-arylcinnolines is likewise independent of the steric configuration of the parent aminoethylenes, the most striking example being that of 4-phenyl-3-methylcinnoline (II; R_1 = Ph; R_2 = Me). Stoermer and Fincke (*Ber.*, 1909, **42**, 3115), who first prepared this substance, obtained a crystalline aminoethylene by dehydration of the carbinol prepared from *o*-aminobenzophenone and ethylmagnesium iodide. The present author, on the other hand, obtained an oily ethylene, which was converted into two crystalline stereoisomeric hydrochlorides. One of these, m. p. 205°, was probably identical with the salt, m. p. 208°, prepared by Stoermer and Fincke from their crystalline aminoethylene, and the other, m. p. 185—198°, was evidently a mixture. However, each salt on diazotisation gave an almost quantitative yield of the cinnoline, clearly proving the irrelevance of steric configuration. In agreement with these observations, oily ethylenes, undoubtedly mixtures of stereoisomers, were encountered in the preparation of 4-p-*anisyl*-3-*methylcinnoline* (II; R_1 = *p*-$MeOC_6H_4$; R_2 = Me), carried out by Mr. C. M. Atkinson in this laboratory, and 3-*phenyl*-4-p-*anisylcinnoline* (II; R_1 = *p*-$MeOC_6H_4$; R_2 = Ph). On the other hand, the ethylene which gives rise to 4-*p*-anisylcinnoline, and in which geometrical isomerism is impossible, crystallises readily as observed by Stoermer and Gaus (*Ber.*, 1912, **45**, 3104) and confirmed in the present work.

Before the suggestion that the Widman–Stoermer reaction involves a polarised molecule of type (I), it was pointed out (Part II) that compounds of type (I) in which R_1 is hydrogen or carboxyl and R_2 is aryl do not yield cinnoline derivatives, and this behaviour is readily understood if reinforcement by R_1 of the C_α–C_β polarisation is essential to the formation of the cinnoline nucleus, as the requisite " T " effect could not be developed when R_1 = H or CO_2H. In order more fully to investigate this point, an examination has been made of the behaviour of two diazonium salts of type (I), in which R_1 = H and R_2 = α-pyridyl and α-quinolyl respectively.

2-(2′-Aminostyryl)pyridine (III; $R_1 = NH_2$; R_2 = α-C_5H_4N) was prepared by Räth and Lehmann (*Ber.*, 1925, **58**, 342) on a small scale, and apparently in varying yield, by reduction of the nitro-compound with zinc dust " in strongly acid solution "; it is however readily obtained in consistently good yield by reduction with iron and acetic acid, a method which is very successful in the preparation of numerous *o*-amino-acetophenones and -benzophenones (*J.*, 1945, 646). The base was readily diazotised; the diazonium salt coupled with β-naphthol, but no cinnoline formation could be observed at room temperature. When the solution was heated, nitrogen was readily evolved and 2-(2′-hydroxystyryl)pyridine (III; R_1 = OH; R_2 = α-C_5H_4N) was formed as main product. Treatment of the diazonium solution with cuprous chloride gave a crystalline covalent copper compound, which was not obtained pure, but on decomposition yielded 2-(2′-*chlorostyryl*)*pyridine* (III; R_1 = Cl; R_2 = α-C_5H_4N). The diazotised aminostilbazole thus shows the normal reactions of a diazonium salt, with no appreciable tendency towards any well-defined ring-closure.

In some respects the behaviour of 2-(2′-aminostyryl)quinoline (III; $R_1 = NH_2$; R_2 = α-C_9H_6N) resembled that of the pyridine derivative. Thus diazotisation of the amine was again facile, and 2-(2′-*chlorostyryl*)-*quinoline* (III; R_1 = Cl; R_2 = α-C_9H_6N) was readily formed in the Sandmeyer reaction, again, apparently, *via* a covalent copper compound. The diazonium salt (in hydrochloric acid) was stable at 5°; when the solution was heated, the main product was 2-(2′-hydroxystyryl)quinoline (III; R_1 = OH; R_2 = α-C_9H_6N), but a noteworthy feature of this reaction was the simultaneous production of considerable amounts of 2-(2′-chlorostyryl)quinoline. The chloro- and hydroxy-styrylquinolines accounted for the bulk of the material used, and there was no evidence of the formation of any cinnoline derivative or other product.

The extent to which the salts (I; R_1 = H; R_2 = α-pyridyl or α-quinolyl) will yield pyridinium or quino-

linium ions under the reaction conditions used is uncertain, but it is improbable that such ions would favour cinnoline formation, because a strongly kationoid centre in R_2 could compete with the diazonium grouping for any available electrons on C_β and thus diminish the extent of cinnoline formation [cf. the production of 2-phenylchrysene as a concomitant of 4-phenyl-3-(1′-naphthyl)cinnoline (*J.*, 1943, 447; 1945, 520)]. It is not considered likely that this effect would entirely inhibit the cinnoline synthesis, the failure of which in the present work is believed to support the mechanism previously advanced (*loc. cit.*), and, in particular, to confirm that the *sine qua non* of the reaction is the attachment to C_α of an electron-donating substituent.

The application of the reaction to the synthesis of 4-methylcinnolines will be discussed in a subsequent paper.

Experimental.

(Melting points are uncorrected.)

4-Phenyl-3-methylcinnoline.—Phenyl-*o*-aminophenylethylcarbinol, m. p. 102—103° (15·6 g.), was obtained from *o*-aminobenzophenone (14 g.) by the method of Stoermer and Fincke (*loc. cit.*). In contrast to the experience of these authors, dehydration of the carbinol [with 15 vols. of a mixture of concentrated sulphuric acid and water (1 : 6, v/v) for ½ hour at 100°] gave a mixture of aminoethylenes which could not be crystallised. Conversion into the hydrochlorides and fractional crystallisation of the mixture from 2N-hydrochloric acid gave a number of fractions of which the least soluble had m. p. 204—205° and was probably identical with the product, m. p. 208°, described by Stoermer and Fincke (Found: C, 73·55; H, 6·4; N, 6·2; Cl, 14·25. Calc. for $C_{15}H_{16}NCl$: C, 73·3; H, 6·55; N, 5·7; Cl, 14·45%). One of the most soluble fractions had m. p. 185—198° (Found: C, 73·65; H, 6·65; N, 6·1; Cl, 14·35%) and was clearly a stereoisomeric mixture. Small-scale experiments showed that each fraction gave a high yield of cinnoline on diazotisation; consequently the total hydrochloride mixture was dissolved in 2N-hydrochloric acid (250 c.c.), cooled in ice, and treated with 10% sodium nitrite (70 c.c.). The crude product obtained by basification of the solution with ammonia contained a little non-basic material; this was removed, either by filtration of a solution of the crude material in hot 2N-hydrochloric acid or by dissolving the crude substance in ether and extracting the cinnoline with dilute hydrochloric acid. The purified cinnoline was crystallised from aqueous alcohol; it formed yellow parallelograms (12·8 g.), m. p. 134—136° (lit., 135—136°) (Found: C, 82·1; H, 5·4; N, 12·7. Calc. for $C_{15}H_{12}N_2$: C, 81·8; H, 5·5; N, 12·7%).

3-Phenyl-4-p-anisylcinnoline.—A Grignard solution from magnesium (7·5 g.), benzyl chloride (44 c.c.), and ether (60 c.c.) was treated with a solution of 2-amino-4′-methoxybenzophenone (15 g.) in ether (150 c.c.), added during 10 minutes at room temperature; heat was evolved, and the mixture refluxed gently. After being refluxed for a further 1½ hours, the product was treated with iced ammoniacal ammonium chloride solution. *2-Aminophenylanisylbenzylcarbinol* readily crystallised (18·3 g., very sparingly soluble in ether); it separated from aqueous alcohol or benzene–ligroin (b. p. 40—60°) in nodules of small soft needles, m. p. 133—134·5° (Found: N, 4·95. $C_{21}H_{21}O_2N$ requires N, 4·4%). Treatment of the carbinol (17·8 g.) with a mixture of concentrated sulphuric acid (50 c.c.) and water (300 c.c.) at 100° for 1 hour, followed by basification with ammonia, yielded the ethylene as a viscous reddish-yellow resin, which was dissolved in acetic acid (50 c.c.). After addition of concentrated hydrochloric acid (30 c.c.) and water (30 c.c.), the clear solution was diazotised at 5° with 10% aqueous sodium nitrite (65 c.c.). The ochre-coloured crystalline hydrochloride which separated had m. p. 216—217° (efferv.), and on basification yielded almost pure *3-phenyl-4-p-anisylcinnoline* (17 g.; m. p. 167—169°), moderately soluble in hot alcohol, from which it separated in yellow jagged needles, m. p. 169—170·5° (Found: C, 81·1; H, 5·3; N, 9·1. $C_{21}H_{16}ON_2$ requires C, 80·75; H, 5·1; N, 9·0%).

4-p-Anisyl-3-methylcinnoline.—The carbinol, prepared as above from 2-amino-4′-methoxybenzophenone (25 g.), magnesium (16·1 g.), ethyl iodide (110 g.), and ether (575 c.c.), was dehydrated, and the product diazotised, in the manner described above. The *cinnoline* (crude, 26 g.) crystallised from aqueous alcohol in yellow leaflets, m. p. 131—133° (Found: C, 77·15; H, 5·45; N, 11·95. $C_{16}H_{14}ON_2$ requires C, 76·8; H, 5·6; N, 11·2%).

2-(2′-Nitrostyryl)pyridine.—Since this work was completed, conditions for the large-scale preparation of this nitrostilbazole have been described by Ruggli and Cuenin (*Helv. Chim. Acta*, 1944, **27**, 649); the material used in the present work was prepared by a modification of the procedure of Shaw and Wagstaff (*J.*, 1933, 77), 5 g. of *o*-nitrobenzaldehyde yielding 4·4 g. of almost pure nitrostilbazole. A bath temperature of 165—170° was necessary; at 135—140° the reaction was incomplete and unreacted aldehyde (1·5 g.) was recovered.

2-(2′-Aminostyryl)pyridine.—A solution of the nitro-compound (5 g.) in glacial acetic acid (40 c.c.) was kept at 90—95° and treated with iron filings (5 g.), added in portions during 1 hour with frequent shaking; three 10 c.c. portions of water were added at the start of the reaction and at half-hourly intervals thereafter. After a total of 80 minutes, the mixture was diluted with water and the amine extracted with ether, the extract being washed with water, aqueous sodium carbonate, and again with water, dried, and evaporated. A solution of the residue in ether–ligroin (b.p. 40—60°) deposited the pure base (3·1 g.) in bright yellow, long, soft needles, m. p. 85—86°, with high power of crystallisation (Räth and Lehmann, *loc. cit.*, give m. p. 98—99°). The substance showed pronounced basic properties, and the yield could probably have been increased by neutralising the acetic acid before extracting the amine. A dilute solution of the base in ether showed a splendid blue fluorescence. The *diacetyl* derivative was obtained by refluxing a solution of the base in 5 parts of acetic anhydride for ½ hour followed by addition of water and evaporation in an exhausted desiccator; it crystallised from ether–ligroin (b. p. 40—60°) in thin colourless rhombs, m. p. 111—112° (Found: C, 72·75; H, 5·55; N, 10·4. $C_{17}H_{16}O_2N_2$ requires C, 72·8; H, 5·75; N, 10·0%).

Reactions of Diazotised 2-(2′-Aminostyryl)pyridine.—No crystalline product could be obtained when a solution of the amine in 2N-hydrochloric acid was diazotised and made alkaline with ammonia. A solution of the amine (800 mg.) in glacial acetic acid (5 c.c.) was treated with concentrated hydrochloric acid (5 c.c.), and the resultant suspension of the hydrochloride was cooled in ice and diazotised with excess (10 c.c.) of 2½% aqueous sodium nitrite; portions of the clear yellow solution thus formed were treated as follows. (i) The solution (8 c.c.) was kept at 5—10° for 40 hours. It still gave a strong coupling reaction with alkaline β-naphthol, and was then heated on the steam-bath; when the brisk evolution of nitrogen ceased the solution was made alkaline with aqueous sodium carbonate, which precipitated a pale sticky resin. A solution of this product in aqueous alcohol deposited crude 2-(2′-hydroxystyryl)pyridine; this was dissolved in warm aqueous sodium hydroxide, and the solution, after filtration from a little insoluble material, was acidified with hydrochloric acid and the excess of acid neutralised by sodium bicarbonate solution. The precipitated hydroxystilbazole, which possessed well-marked amphoteric properties, crystallised from aqueous alcohol in colourless hexagonal plates, m. p. 143—144° (Found: C, 79·15; H, 5·7; N, 7·2. Calc. for $C_{13}H_{11}ON$: C, 79·1; H, 5·6; N, 7·1%). Chiang and Hartung (*J. Org. Chem.*, 1945, **10**, 21) give m. p. 125° and 130—132° for unanalysed samples; Butter (*Ber.*, 1890, **23**, 2697) gives m. p. 132°; both sets of workers prepared this substance from α-picoline and salicylaldehyde.

(ii) A portion of the diazotised solution (6 c.c.) was diluted with water (18 c.c.), kept at 5—10° for 40 hours, treated with sodium acetate until neutral to Congo-red, and then left at room temperature. Gassing occurred for some days, and a high-melting, amorphous solid was precipitated, from which no crystalline product could be obtained by means of organic solvents, hydrochloric acid, or sodium hydroxide.

(iii) The remainder (6 c.c.) of the solution was added during 2—3 minutes to a solution of cuprous chloride (2 g.) in concentrated hydrochloric acid (8 c.c.) and water (6 c.c.); immediate effervescence and separation of solid occurred, and after the addition of more water (4 c.c.) the mixture was kept at 70—80° for 10 minutes and filtered cold. The solid (A) was a copper-containing complex. In a second experiment, crude (A) was recrystallised from hot 2N-hydrochloric acid, yielding pale yellow needles (1·5 g. from 1 g. of amine), m. p. 120—123° after being dried in an evacuated desiccator: the substance turned green on exposure to air. When boiled with water, (A) was converted into a new substance (B), m. p. 184—186°, apparently insoluble in water, alcohol, acetone, and acetic acid; (B), like (A), contained copper. A solution of (B) in warm pyridine gave a precipitate of 2-(2′-*chlorostyryl*)*pyridine* on addition of water; the filtrate contained chloride ions, but only a trace of chloride ion could be detected in the filtrate from a suspension of (B) in boiling water. Decomposition of (B) to the chlorostyrylpyridine could also be effected with aqueous ammonia, and (incompletely) by means of aqueous dioxan. A solution of (B) in 2N-hydrochloric acid did not regenerate (A), but deposited what appeared to be the *hydrochloride* of the chlorostyrylpyridine in fine, almost colourless needles, m. p. 184—186° after prolonged drying [strongly depressed by admixture with (B)] (Found: C, 54·45; H, 4·75; Cl, 24·7. $C_{13}H_{11}NCl_2,2H_2O$ requires C, 54·15; H, 5·2; Cl, 24·65%). The free chlorostyrylpyridine was most simply prepared by treating a hot solution of (A) (0·8 g.) in very dilute nitric acid with excess of ammonia; the resultant solid was filtered off, washed and crystallised from aqueous ammoniacal alcohol, from which the base (0·45 g.) formed colourless, lustrous, prismatic needles, m. p. 77—78° (Found: C, 72·35; H, 4·7; Cl, 16·45. $C_{13}H_{10}NCl$ requires C, 72·4; H, 4·7; Cl, 16·5%). A specimen of hydrochloride, prepared from this base by solution in moderately concentrated hydrochloric acid and evaporation in an exhausted desiccator, had almost the same m. p. (182—183°) as that previously described, but a mixture of the two samples melted at 165—170°. This result may possibly be due to hydration of one or the other sample.

2-(2′-*Aminostyryl*)*quinoline*.—This was prepared from the nitro-compound, but much unchanged material was recovered when the conditions of Maurer and Stark (*Ber.*, 1937, **70**, 2054) were followed. This was due to the insolubility of the nitro-compound in the acid mixture recommended by these authors, and reduction proceeded smoothly when the nitro-compound was dissolved in a hot mixture of acetic acid, 2N-hydrochloric acid, and concentrated hydrochloric acid (2 : 2 : 1 by volume). This solution was then treated according to the procedure of Maurer and Stark; 8·2 g. of nitro-compound yielded 6 g. of amine, m. p. 157—158°.

Reactions of Diazotised 2-(2′-*Aminostyryl*)*quinoline*.—(a) The deep red solution formed by warming the amine (1·5 g.) with glacial acetic acid (7·5 c.c.) was cooled and treated with concentrated hydrochloric acid (5 c.c.), and the resultant suspension was diazotised with aqueous sodium nitrite (4·8 c.c. of 10%). Part (5·5 c.c.) of the clear yellow solution thus formed was added to a solution of cuprous chloride [prepared from 4·4 g. of copper sulphate crystals (*Org. Synth.*, Coll. Vol. I., p. 170)] in concentrated hydrochloric acid (10 c.c.); rapid reaction occurred with separation of a solid, and the temperature rose to 30—35°. After ¼ hour at 75—80°, the mixture was left at room temperature for 48 hours, and finally boiled for 5 minutes and filtered. The solid was apparently a covalent copper compound (cf. the pyridine derivative already described), as it was impossible to free it from copper by washing with hydrochloric acid and water. Decomposition with aqueous ammonia and crystallisation from ammoniacal alcohol yielded solvated crystals of 2-(2′-*chlorostyryl*)-*quinoline*, which after being dried and crystallised from ethyl acetate–ligroin (b. p. 40—60°) formed almost colourless hard nodules of prismatic needles, m. p. 78—79° (Found: C, 77·0; H, 4·65; Cl, 13·1. $C_{17}H_{12}NCl$ requires C, 76·8; H, 4·6; Cl, 13·4%).

(b) When the diazotised solution was heated, mixtures of the foregoing chloro-compound and the corresponding phenol were produced. Dilution of the solution with varying amounts of water, followed either by immediate heating or by heating after keeping the solution for a week at 5°, had no effect, qualitatively, on the result: the effect of these variations on the proportion of chloro-compound to phenol was not studied, but the phenol predominated. A typical experiment was the following. The diazotised solution (from 1·5 g. of amine) was heated for ¼ hour at 80—85° without dilution with water. The solution was then evaporated to dryness in an exhausted desiccator, after which the residue was partitioned between 5% aqueous sodium hydroxide and ether; the latter yielded 1·07 g. of resinous material (A). Acidification of the alkaline extract with dilute hydrochloric acid gave 0·3 g. of crude phenol, which was freed from hydrochloride by solution in aqueous sodium hydroxide, addition of acetic acid, and precipitation with aqueous ammonia. Crystallisation from ammoniacal alcohol and finally from alcohol or ethyl acetate yielded 2-(2′-hydroxystyryl)quinoline in soft yellow needles (alcohol) or small, brittle prisms (ethyl acetate), m. p. 212—213° (Found: C, 82·3, 82·65; H, 5·6, 5·4; N, 5·85, 6·1. Calc. for $C_{17}H_{13}ON$: C, 82·5; H, 5·3; N, 5·7%); Wallach and Wüsten (*Ber.*, 1883, **16**, 2009), and Dzierzgowski (*ibid.*, 1894, **27**, 1980), who prepared this substance from quinaldine and salicylaldehyde, give m. p. 209—210° and 209° respectively. The substance is insoluble in ammonia and moderately soluble in aqueous sodium hydroxide; it showed marked basic properties, yielding a soluble acetate and a sparingly soluble deep yellow hydrochloride (with cold dilute hydrochloric acid). The *acetoxy*-compound (acetic anhydride; reflux) was isolated from weakly ammoniacal solution. After crystallisation from aqueous alcohol, and finally from ligroin (b. p. 60—80°), it formed faintly yellow clusters of stout prismatic needles, m. p. 89—90° (Found: C, 78·7; H, 5·15. $C_{19}H_{15}O_2N$ requires C, 78·8; H, 5·2; N, 4·8%). The same substance was produced when the phenol hydrochloride was refluxed with acetic anhydride for 1—1½ hours, but the yield was smaller, and the product (m. p. 92—94°) could not be obtained pure (Found: C, 79·45; H, 5·55; N, 5·45%).

Owing to the somewhat sparing solubility of the foregoing phenol in aqueous sodium hydroxide, the "neutral" fraction (A) contained much of this substance. Crystallisation of 1·27 g. of this mixture from a little ethyl acetate gave 0·4 g. of nearly pure phenol. The mother liquor was evaporated to dryness, and the residue treated with a hot alcoholic solution of picric acid (1 g.); 1·25 g. of the crude *picrate*, m. p. 212—218°, of 2-(2′-chlorostyryl)quinoline separated, m.p. 236—237° after crystallisation from methyl ethyl ketone, in which it is sparingly soluble, separating in small, soft, bright yellow, lustrous needles (Found: C, 55·85; H, 3·55; N, 11·35. $C_{17}H_{12}NCl,C_6H_3O_7N_3$ requires C, 55·8; H, 3·05; N, 11·3%). Decomposition of this picrate with either ammonia or sodium hydroxide, followed by ether-extraction, etc., gave the crude chloro-base as a resin. A portion of this material was treated with dilute hydrochloric acid; the precipitated *hydrochloride*, very sparingly soluble in dilute hydrochloric acid, crystallised from acetic acid–ether in long, ochre-coloured needles, m. p. 248—251° (Found: N, 4·85; Cl, 22·8. $C_{17}H_{12}NCl_2$ requires N, 4·6; Cl, 23·5%). The remainder of the resin was treated with hot ligroin (b. p. 60—80°); the solution was decanted from a little insoluble matter, clarified with charcoal, and concentrated, yielding 2-(2′-chlorostyryl)quinoline, m. p. 77—78° alone and mixed with the sample described in (a), and giving a positive Beilstein reaction (Found: C, 76·85; H, 4·7; N, 5·4. $C_{17}H_{12}NCl$ requires C, 76·8; H, 4·6; N, 5·3%).

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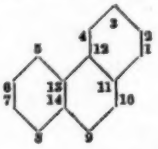
139. *Experiments on the Synthesis of Substances Related to the Sterols. Part XLV.*

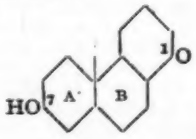
By J. W. Cornforth and (Sir) Robert Robinson.

The use of a naphthalene derivative to provide rings B and C of the sterol skeleton has advantages. In the investigation initiated by this memoir the ring A is added and a reactive group left in ring C which will facilitate the construction of ring D at a later stage.

The preparation of the tricyclic intermediate ABC is described and, making use of recognised analogies, it is pointed out that the stereochemical configuration is favourable apart from one dubiety.

The starting point is 1 : 6-dihydroxynaphthalene, and the tricyclic products may be endowed with various functional groups of which the most significant is perhaps the keto-alcohol (I).



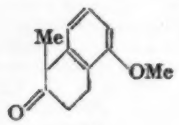


(I.)

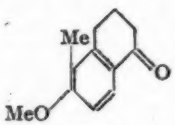
Evidence will shortly be submitted that the attempt of Martin and Robinson (*J.*, 1943, 497) to synthesise a stereoisomeride of androstendione broke down at the last stage, because the addition of a ring to the BCD intermediate did not proceed so as to give ABCD, which would have been structurally identical with androstendione, but afforded BCDE. Variations of this method are being studied in order to overcome the obstacle, *e.g.*, one in which the elements necessary for D are introduced but not developed into the cyclic ketone until A is added, and another in which the tricyclic intermediate (BCD) is not employed as heretofore as a diketone, but as a keto-alcohol. In any case the configurational aspects of this route are not sufficiently under control and for this reason we have devoted attention to another route, somewhat similar in character, but thought to be more precise stereochemically. It transpires that the new order of the stages has decided preparative advantages in addition.

The precedent researches are on the one hand those of Du Feu, McQuillin, and Robinson (Part XIV, *J.*, 1937, 53) and Robinson and Weygand (Part XXX, *J.*, 1941, 386) which showed that nascent methyl vinyl ketone (from the metho-salt of a methyl β-dialkylaminoethyl ketone) condenses with 2-methyl*cyclo*hexanone or with 1-methyl-2-decalone at the methine group bearing the methyl substituent in preference to the methylene group adjacent to carbonyl.

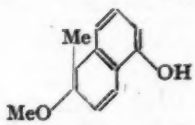
On the other hand the present authors have described a convenient method for the preparation of 2-tetralones from the 2-naphthols. In the course of this work (*J.*, 1942, 689) we mentioned the production of 5-methoxy-1-methyl-2-tetralone (II), isolated as the semicarbazone, from 6-methoxy-5-methyl-1-tetralone (III), which is the ketone used by Martin and Robinson (*loc. cit.*) as a starting point and prepared by them from β-naphthol.



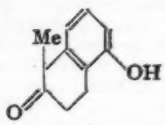
(II.)



(III.)



(IV.)



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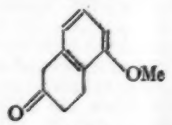
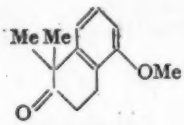


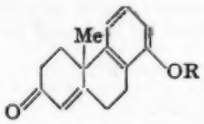
(VI.)

The preparation of II from III has been re-examined. 6-*Methoxy*-5-*methyl*-1-*naphthol* (IV) was isolated from the products of dehydrogenation of III with sulphur. The naphthol was reduced with sodium and alcohol, using a liquid ammonia medium (cf. Birch, *J.*, 1944, 434), and, after hydrolysis of the unstable enol ether, 5-hydroxy-1-methyl-2-tetralone (V) was obtained. This was readily methylated to II. The overall yield, though slightly better than before, was not encouraging.

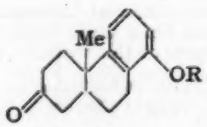
In our previous communication (*loc. cit.*) we described the preparation of 5-methoxy-2-tetralone (VI) from 1 : 6-dihydroxynaphthalene. On methylation of VI with methyl iodide–sodium *iso*propoxide, the dimethylated ketone (VII) was the only product that could be isolated. We have now repeated, and have been able to improve, the preparation of VI. Since the production of VII in quantity indicates that the ketone (II) is unexpectedly reactive, we tried the methylation in methanol instead of in *iso*propanol, the object being to suppress the formation of anions from II. Under these conditions, a mixture of the ketones (VI), (VII), and (chiefly) (II) resulted. The separation of these might well have been difficult, but we found that II combines with sodium bisulphite slowly, whereas VI reacts quickly and VII not at all. Taking advantage of this observation, the isolation of the three ketones was easy. The identity of the ketone (II) with that previously prepared was established by comparison of the semicarbazones. This provides, incidentally, an additional proof of the structure of the α-tetralone (III).



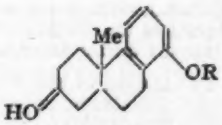
(VII.)



(VIII.)



(IX).



(X.)

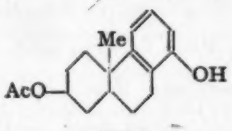
The unusually high acidity of II facilitated the preparation of a sodium enolate, a few minutes' treatment with sodamide in cold benzene being sufficient. Reaction of the enolate with 4-diethylaminobutan-2-one methiodide gave 7-*keto*-1-*methoxy*-13-*methyl*-5 : 6 : 7 : 9 : 10 : 13-*hexahydrophenanthrene* (VIII; R = Me) in 55% yield. We even expect to be able to improve this result, but it is already an unusually favourable case of this type of ring system extension.

The stepwise catalytic reduction of VIII (R = Me) in alcoholic solution gave successively 7-*keto*-1-*methoxy*-13-*methyl*-5 : 6 : 7 : 8 : 9 : 10 : 13 : 14-*octahydrophenanthrene* (IX; R = Me) and 7-hydroxy-1-methoxy-13-methyl-5 : 6 : 7 : 8 : 9 : 10 : 13 : 14-octahydrophenanthrene (X; R = Me). The latter was obtained as a mixture of epimers, one of which has been isolated in a pure condition. Dehydrogenation of X with selenium followed by demethylation gave 1-phenanthrol; a proof that the ring extension takes the direction illustrated in the formulae.

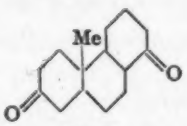
Demethylation of VIII (R = OMe) was effected rather smoothly by a dilute solution of hydrogen iodide in acetic acid. The resulting 1-*hydroxy*-7-*keto*-13-*methyl*-5 : 6 : 7 : 9 : 10 : 13-*hexahydrophenanthrene* (VIII; R = H) on reduction in neutral solution afforded 1-*hydroxy*-7-*keto*-13-*methyl*-5 : 6 : 7 : 8 : 9 : 10 : 13 : 14-*octahydrophenanthrene* (IX; R = H). This was isolated through the bisulphite compound: since it was thus obtained directly in a pure state, and no stereoisomeric ketone could be detected, it is very probable that the hydroaromatic rings are fused in the *cis*-form (cf. reductions of cholestenone and 2-keto-9-methyl-$\Delta^{1:10}$-octalin).

The reduction of IX (R = H) in acetic acid solution gave a mixture of epimers, but one predominated and was easily obtained pure. This 1 : 7-*dihydroxy*-13-*methyl*-5 : 6 : 7 : 8 : 9 : 10 : 13 : 14-*octahydrophenanthrene* (X; R = H) has probably, by analogy with the sterols, a *cis* relationship of the hydroxyl and angular methyl groups, and thus belongs to the *normal*, rather than the *epi*, series. The diol (X; R = H) was also obtained by direct reduction of VIII (R = H) and, though in poor yield, by demethylation of X (R = Me).

Treatment of the diol (X; R = H) with a slight excess of acetic anhydride, using potassium acetate as a catalyst and acetic acid as solvent, gave 1-*hydroxy*-7-*acetoxy*-13-*methyl*-5 : 6 : 7 : 8 : 9 : 10 : 13 : 14-*octahydrophenanthrene* (XI), the phenolic group remaining free. The monoacetate (XI) was hydrogenated over platinum in warm acetic acid, when hydrogen corresponding to three molecular proportions was absorbed. The product, without isolation, was oxidised with chromium trioxide in acetic acid and refluxed with alcoholic potash. The purpose of the latter operation was not only to remove the acetoxyl group, but also to rearrange any *cis*-α-decalones present to the *trans* form (cf. Hückel, *Annalen*, 1925, **441**, 1). The resulting product contained 7-hydroxy-1-keto-13-methyltetradecahydrophenanthrene (I) which was readily isolated as the sparingly soluble *semicarbazone*.



(XI.)



(XII.)

We have already expressed our view of the stereochemical relationship between carbon atoms 7, 13, and 14. As regards the positions 11 and 12, the method of preparation makes it probable that they are part of a *trans*-α-decalone; it is hard to decide which of the two possible *trans* forms would arise. It seems likely, therefore, that in the ketone (I) the five asymmetric carbon atoms have either the same relative configuration as is found in coprosterol, or the form, otherwise the same, in which rings B and C have the alternative linkage of the *trans* type.

In one experiment on the reduction of the phenolic ketone (VIII; R = H) with platinum and hydrogen, a small amount of neutral product was obtained. This was oxidised with chromic acid and converted into the 2 : 4-dinitrophenylhydrazone. From the resulting mixture (probably of mono- and bis-derivatives) a small quantity of a sparingly soluble derivative was isolated, which appeared to be the *bis*-2 : 4-*dinitrophenylhydrazone* of 1 : 7-*diketo*-13-*methyltetradecahydrophenanthrene*.

Experimental.

6-*Methoxy*-5-*methyl*-1-*naphthol* (IV).—6-Methoxy-5-methyl-1-tetralone (43 g.) was dehydrogenated with sulphur as previously described (*loc. cit.*). The product was treated with benzene and charcoal, and the naphthol extracted from the filtered solution with 2N-sodium hydroxide. The neutral fraction was again heated with sulphur and worked up as before. On acidification of the alkaline extracts the *naphthol* separated; it was purified by distillation [180° (bath temp.)/0·2 mm.] and crystallisation from benzene, giving 26 g., m. p. 138—141°. Another crystallisation from benzene gave colourless needles, m. p. 142—143° (Found: C, 76·3; H, 6·4. $C_{12}H_{12}O_2$ requires C, 76·6; H, 6·4%).

5-*Hydroxy*-1-*methyl*-2-*tetralone* (V).—The naphthol (IV) (40 g.) suspended in liquid ammonia (300 c.c.) and ethanol (27 c.c.) was reduced by the gradual addition of sodium (10·5 g.). When reaction was complete the solvent was removed and the residue dissolved in water (500 c.c.). (Passage of carbon dioxide at this point precipitated the enol ether, which crystallised from light petroleum in long needles, m. p. *ca.* 110°, but apparently had already suffered slight hydrolysis.) Hydrochloric acid was now added, sufficient to make the solution 1N with respect to it. A little benzene was added and the solution shaken for a short time, then cooled and treated with light petroleum (b. p. 40—60°). The product crystallised at once; it was collected next day, washed with water, then with benzene–light petroleum (1 : 2), dried, and extracted (Soxhlet) with light petroleum (b. p. 40—60°) for several hours. The residue (28 g.) then had m. p. about 120° with previous softening, and was used for the methylation. A sample recrystallised from benzene gave the *hydroxy-ketone* in aggregates of leaflets, m. p. 127—128° (Found: C, 75·0; H, 6·9. $C_{11}H_{12}O_2$ requires C, 75·0; H, 6·8%). This ketone did not afford a sodium bisulphite compound.

Methylation of 5-*Hydroxy*-1-*methyl*-2-*tetralone*.—The crude hydroxy-ketone (29·5 g.) was dissolved in sodium hydroxide

(10% excess of 2N) and shaken with methyl sulphate (5% excess), with gentle warming on the steam-bath. After 2 hours the cooled mixture was made strongly alkaline and extracted with ether. The ethereal solution was concentrated to about 60 c.c. and shaken with saturated sodium bisulphite solution (180 c.c.), for 9 hours. The solid additive compound began to separate after about an hour. It was collected, washed with ether, and decomposed by sodium carbonate in the presence of ether. The *methoxy-ketone* (II) distilled almost without residue at 102°/0·1 mm., as a colourless viscid oil (17 g.), $n_D^{16\cdot6°}$ 1·5559 (Found: C, 75·4; H, 7·5. $C_{13}H_{14}O_2$ requires C, 75·8; H, 7·4%). The semicarbazone, crystallised from alcohol, had m. p. 188—190°, alone or mixed with an authentic specimen. From the ether washings of the bisulphite compound 2 : 5-dimethoxy-1-methylnaphthalene was recovered, m. p. 85° after crystallisation from alcohol. This of course arose from the naphthol (IV) which had escaped reduction in the previous stage.

Methylation of 5-Methoxy-2-tetralone (VI).—The ketone (9·7 g.; prepared in 70% overall yield from 1 : 6-dihydroxynaphthalene) was added to a solution of sodium (1·26 g.) in methanol (25 c.c.) under nitrogen. Methyl iodide (12 g.; 50% excess) was added at once with ice-cooling; the mixture was then allowed to warm spontaneously and finally refluxed for a few minutes. A few drops of dilute sulphuric acid were added and the nitrogen stream was stopped. Water was added and most of the methanol removed. The product was extracted with ether, and the ethereal solution concentrated to about 40 c.c. and shaken with small successive quantities of sodium bisulphite solution until the ethereal solution no longer gave the " tetralone-blue " reaction. The ether was then removed and the residue shaken overnight with fresh sodium bisulphite solution. The crystalline product from the last extraction was collected, washed well with ether, and decomposed with sodium carbonate, giving the monomethyl ketone (II) (3·65 g.), b. p. 102°/0·1 mm. The first sodium bisulphite washings, worked up in the same way, gave the unchanged ketone (VI) (2·4 g.). The ethereal solution of material which did not react with sodium bisulphite crystallised on evaporation and consisted chiefly of the dimethyl ketone (VII) which was obtained in large rhombic plates (1 g.) on crystallisation from light petroleum. The monomethyl ketone (II) was converted into the semicarbazone, which, crude, had m. p. 182—184°, raised by one crystallisation from alcohol to 188—190° (Found: C, 63·1; H, 7·0. Calc. for $C_{13}H_{17}O_2N_3$: C, 63·2; H, 6·9%). The m. p. was undepressed by admixture with a specimen prepared as described previously (*loc. cit.*).

It was found that methylation using sodium *iso*propoxide also gave the ketone (II), but here the yield was lower owing to more of the dimethyl ketone being formed.

7-Keto-1-methoxy-13-methyl-5 : 6 : 7 : 9 : 10 : 13-hexahydrophenanthrene (VIII; R = Me).—The diethylaminobutanone methiodide used was prepared according to Wilds (*J. Amer. Chem. Soc.*, 1943, **65**, 471); in our experience it invariably crystallised, provided that the methyl iodide was not added too rapidly.

5-Methoxy-1-methyl-2-tetralone (2·5 g.) was added under nitrogen to a suspension of sodamide (1·05 g.) in benzene (15—20 c.c.). The mixture was shaken in a cold water-bath for 15 minutes. A suspension of diethylaminobutanone methiodide (from 2 g. of the Mannich base) in *iso*propanol (*ca.* 10 c.c.) was added from a hopper. After being shaken in cold water for 15 minute and refluxed gently for a further 15 minutes, the mixture was cooled and treated with dilute sulphuric acid (20 c.c. of 2N). The benzene layer was washed with water and the solvents removed. The residue on distillation gave 2·45 g., nearly all b. p. 160—170°/0·1 mm. The distillate was very viscous, the higher fractions being glassy when cold. The whole was dissolved in ether, concentrated to 6 c.c., and kept at 0° for 2 days. The crystals were washed by decantation with chilled ether and collected (1·6 g.). A small further quantity could be obtained by fractional distillation of the mother liquors. The product so obtained was almost pure; crystallisation from light petroleum (b. p. 40—60°) gave the *methoxy-ketone* in colourless prisms, m. p. 119—120° (Found: C, 79·4; H, 7·2. $C_{16}H_{18}O_2$ requires C, 79·3; H, 7·4%).

The 2 : 4-*dinitrophenylhydrazone* crystallised from dioxan–alcohol in stout, red, four-sided prisms, m. p. 239—242° (decomp.) (Found: N, 13·1. $C_{22}H_{22}O_5N_4$ requires N, 13·3%).

7-Keto-1-methoxy-13-methyl-5 : 6 : 7 : 8 : 9 : 10 : 13 : 14-octahydrophenanthrene (IX; R = Me).—The unsaturated ketone (VIII; R = Me) (400 mg.) in alcohol (10 c.c.) was hydrogenated at 15°/1 atm. over platinum oxide (20 mg.). One mol. of hydrogen was absorbed within 20 minutes; hydrogenation then slowed down greatly and was interrupted. After removal of catalyst and solvent the residue was dissolved in hot light petroleum (b. p. 60—80°) and the solution filtered. Next day the product (300 mg.) was collected; it had m. p. 115—117°, sharply depressed by the ketone VIII (R = Me). One crystallisation from ether gave the *ketone* in stout colourless prisms, m. p. 120—121° (Found: C, 78·8; H, 8·5. $C_{16}H_{20}O_2$ requires C, 78·7; H, 8·2%). Unlike the ketone (VIII; R = Me) the molten substance crystallised at once on cooling.

7-Hydroxy-1-methoxy-13-methyl-5 : 6 : 7 : 8 : 9 : 10 : 13 : 14-octahydrophenanthrene (X; R = Me).—The ketone (IX; R = Me) (2·5 g.) was hydrogenated at 15°/1 atm. in alcohol (50 c.c.) over platinum oxide (220 mg.). The absorption of hydrogen (one mol.) was complete in an hour. The *product* (2 g.) separated from light petroleum (b. p. 40—60°) in colourless rosettes of fine needles, m. p. 110—112°, softening from 105° (Found: C, 77·6; H, 9·0. $C_{16}H_{22}O_2$ requires C, 78·0; H, 9·0%). The mother liquors were united with a further quantity (0·25 g.) prepared by hydrogenating the mother liquors of the ketone (IX; R = Me), boiled with charcoal, and filtered. On cooling, colourless needles were deposited (0·35 g.), melting sharply at 104—105°. This is apparently one epimer of the *alcohol* (X; R = Me) (Found: C, 77·8; H, 8·8%).

Dehydrogenation of the Alcohol (X; R = Me).—The alcohol (1 g., mixed epimers) was heated with selenium (1·5 g.) at 300—310° for 8 hours. The benzene-soluble fraction was distilled up to 190° (bath temp.)/0·02 mm., and the distillate (0·3 g.) refluxed for an hour with acetic acid (1 c.c.) and hydriodic acid (1 c.c.; *d* 1·7). The phenolic product was separated as usual, crystallised from light petroleum (b. p. 80—100°), sublimed at 115°/0·02 mm., and crystallised again, being obtained as colourless, feathery needles, m. p. 152—153° (Found: C, 86·0; H, 5·1. Calc. for $C_{14}H_{10}O$: C, 85·7; H, 5·5%). Fieser (*J. Amer. Chem. Soc.*, 1929, **51**, 2484) gives m. p. 156° for 1-phenanthrol. A few mg. of an authentic specimen prepared by Professor G. R. Clemo were kindly supplied by the Research Department, Imperial Chemical Industries, Ltd., Dyestuffs Division. This was mixed with an equal quantity of our product and the whole completely sublimed, m. p. 153°. The following reactions were noted with the two specimens. On warming with chloroform, alcohol and a little potassium hydroxide a bluish-green coloration develops; on the addition of water the green colour remains in the chloroform layer. The colour of a sulphuric acid solution is orange-yellow to yellow.

The picrate separated from aqueous-alcoholic solution in red needles, m. p. 178—180° (not recrystallised) (Fieser, *loc. cit.*, m. p. 182° from methanol).

1-Hydroxy-7-keto-13-methyl-5 : 6 : 7 : 9 : 10 : 13-hexahydrophenanthrene (VIII; R = H).—The methoxy-ketone (VIII; R = Me; 1·2 g.) was boiled for ½ hour with acetic acid (18 c.c.) and hydriodic acid (1·8 c.c.; *d* 1·7). The mixture was poured into water containing a little sodium bisulphite and the product extracted with ether. Acetic acid was removed by washing with bicarbonate and the phenol then extracted with 2N-sodium hydroxide which was acidified immediately after separation. The neutral part was treated in the same way with proportionate amounts of acetic and hydriodic acid, and the process was repeated with the neutral fraction surviving the second demethylation. The crystalline phenolic precipitates were united and sublimed at 160—200°/0·1 mm., giving a yellow crystalline powder (810 mg.). A sample was crystallised from toluene before sublimation, then sublimed and washed with benzene, giving the *phenol* (VIII; R = H) in minute crystals, m. p. 208—210° with reddening from 200° (Found: C, 78·5; H, 7·0. $C_{15}H_{16}O_2$

requires C, 78·9; H, 7·0%). The 2 : 4-dinitrophenylhydrazone crystallised from aqueous alcohol in dark red prisms decomposing at about 245°.

1-*Hydroxy*-7-*keto*-13-*methyl*-5 : 6 : 7 : 8 : 9 : 10 : 13 : 14-*octahydrophenanthrene* (IX; R = H).—The phenolic ketone (VIII; R = H; 590 mg.) and platinum oxide (30 mg.) were suspended in alcohol (10 c.c.). Hydrogenation at 15°/1 atm. was rapid, one mol. being absorbed in 15 minutes. The reaction was then interrupted and the residue after removal of catalyst and solvent taken up in a little benzene. Next day the crystals (200 mg.) were collected. By shaking the mother liquors in ether with sodium bisulphite solution and decomposition of the resulting insoluble adduct with sodium carbonate, a further quantity (200 mg.) of the same product was obtained. The product sublimed without residue at 160°/0·02 mm. A sample, crystallised from much benzene, gave the *ketone* (IX; R = H) in irregular, colourless prisms, m. p. 190—191° (Found: C, 77·9; H, 7·9. $C_{15}H_{18}O_2$ requires C, 78·2; H, 7·8%). When the phenolic ketone was dissolved in alcohol before hydrogenation, an inferior yield resulted.

1 : 7-*Dihydroxy*-13-*methyl*-5 : 6 : 7 : 8 : 9 : 10 : 13 : 14-*octahydrophenanthrene* (X; R = H).—The ketone (IX; R = H) (0·6 g.) in acetic acid (6 c.c.) was hydrogenated at 15°/1 atm. over platinum oxide (40 mg.). One mol. of hydrogen was taken up in an hour. The solvent and catalyst were removed and the residue was taken up in chloroform. Next day the colourless four-sided tabular crystals (0·4 g.) were collected; the *diol* (X; R = H) had m. p. 170—171° (Found: C, 77·2; H, 8·7. $C_{15}H_{20}O_2$ requires C, 77·6; H, 8·6%). The same product was obtained by hydrogenating the ketone (VIII; R = H) in acetic acid, or by demethylating the methoxy-alcohol (X; R = Me; mixture of epimers). The diol (X; R = H) crystallised from benzene in large solvated prisms, which melted indefinitely and retained solvent with great tenacity.

1-*Hydroxy*-7-*acetoxy*-13-*methyl*-5 : 6 : 7 : 8 : 9 : 10 : 13 : 14-*octahydrophenanthrene* (XI).—The diol (X; R = H; 480 mg.) was boiled for 1 hour with acetic acid (1 c.c.), acetic anhydride (0·24 c.c.), and a few crystals of potassium acetate. On cooling, the product (360 mg.) separated, m. p. 193—194°. Recrystallisation from acetic acid gave the *acetoxy-phenol* (XI) in colourless aggregated prisms, m. p. 196—197° (Found: C, 74·1; H, 7·9. $C_{17}H_{22}O_3$ requires C, 74·4; H, 8·0%). The crystals did not dissolve appreciably in aqueous alkali, but, when an alcoholic solution was precipitated by water, the resulting milky suspension cleared instantly on adding a drop of sodium hydroxide solution.

7-*Hydroxy*-1-*keto*-13-*methyltetradecahydrophenanthrene Semicarbazone*.—The acetoxy-phenol (XI; 360 mg.) with platinum oxide (150 mg.) suspended in acetic acid (3 c.c.) was hydrogenated at ~40°/1 atm. The sparingly soluble phenol gradually dissolved as reduction proceeded. The reduction slackened after the absorption of nearly three mols. of hydrogen (18 hours). Ether was added and the filtered solution washed twice with water and thrice with 5 c.c. portions of 2N-sodium hydroxide. The last two washings gave a slight turbidity on acidification. The ether was removed and the residue (340 mg.; colourless gum) dissolved in acetic acid (8 c.c.) and treated with a solution of chromium trioxide (130 mg.) in acetic acid (2·6 c.c.). After 36 hours water and ether were added, and the ether solution successively washed with water, 2N-alkali, again water, and evaporated. The residue was boiled with alcoholic potash (6 c.c. of N) for 1 hour; the ether-soluble product was then separated from the dark alkaline solution. An attempt to obtain a bisulphite compound proving fruitless, the product was distilled up to 180° (bath temp.)/0·05 mm., the distillate (100 mg.) being taken in two approximately equal fractions. The higher fraction was analysed (Found: C, 77·2; H, 10·4. $C_{15}H_{24}O_2$ requires C, 76·3; H, 10·2%). This indicated that only a slight amount of deoxygenation had taken place. The total distillate was treated with cold aqueous-alcoholic semicarbazide acetate (from 100 mg. of hydrochloride) in the usual manner. Crystallisation set in rapidly. Next day the product (45 mg.) was collected. Recrystallisation from much *iso*butanol gave the *semicarbazone* in small colourless, diamond-shaped prisms, m. p. 244° (decomp.) (Found: C, 65·5; H, 9·3. $C_{16}H_{27}O_2N_3$ requires C, 65·5; H, 9·2%).

1 : 7-*Diketo*-13-*methyltetradecahydrophenanthrene Bis*-2 : 4-*dinitrophenylhydrazone*.—In an early experiment the ketone (VIII; R = H; 180 mg.) with platinum oxide (40 mg.) in acetic acid (3 c.c.) was hydrogenated for 18 hours at ~15°/1 atm. The product was separated into phenolic (110 mg.) and neutral (60 mg.) fractions. From the phenolic part the diol (X; R = H) was isolated. The neutral part was treated with chromium trioxide (52 mg.) in acetic acid (2·6 c.c.). After 36 hours the product, worked up for neutral material as usual, was distilled at 10 mm. and treated with 2 : 4-dinitrophenylhydrazine sulphate in alcohol. Crystallisation first from dioxan and then from dimethylformamide gave yellow, microscopic leaflets, m. p. 255—258° (decomp.) (2 mg.). Analysis was carried out on 1·8 mg. of *substance* (Found: C, 55·2; H, 5·6. $C_{27}H_{30}O_8N_8$ requires C, 54·6; H, 5·1%).

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140. *The Preparation of* o- *and* p-*Nitroacetophenone.*

By A. H. FORD-MOORE and H. N. RYDON.

Two convenient preparative procedures, starting from phenylmethylcarbinol and ethylbenzene respectively, are described.

THE principal product of the nitration of acetophenone is *m*-nitroacetophenone, which may readily be prepared in this way (Morgan and Moss, *J. Soc. Chem. Ind.*, 1923, **42**, 461T; Elson, Gibson, and Johnson, *J.*, 1930, 1128); much *o*-nitroacetophenone is also produced in the nitration but cannot be isolated from the reaction product in good yield or in a satisfactory state of purity. We have accordingly investigated other methods for preparing *o*- and *p*-nitroacetophenone.

Both compounds can be prepared by the classical acetoacetic ester synthesis from the corresponding nitrobenzoyl chlorides (Gevekoht, *Annalen*, 1883, **221**, 323; Needham and Perkin, *J.*, 1904, **85**, 148; Kermack and Smith, *ibid.*, 1929, 814). This method gives products of high purity and we have been able, by its use, to obtain *o*-nitroacetophenone for the first time as a solid, m. p. 24·5°; it is, however, not well suited for the preparation of even moderately large quantities and we have developed two other methods which are preferable in this respect.

The first of these methods starts from phenylmethylcarbinol:

$$Ph{\cdot}CH(OH){\cdot}Me \longrightarrow \underset{(o \text{ and } p)}{NO_2{\cdot}C_6H_4{\cdot}CH(OAc){\cdot}Me} \longrightarrow NO_2{\cdot}C_6H_4{\cdot}CH(OH){\cdot}Me \longrightarrow NO_2{\cdot}C_6H_4{\cdot}CO{\cdot}Me$$

The nitration of phenylmethylcarbinol does not appear to have been studied previously; the procedure we

adopted was nitration with 1·1 mols. of fuming nitric acid in acetic anhydride solution (cf. the nitration of β-phenylethyl alcohol; Sabetay, Bléger, and de Lestrange, *Bull. Soc. chim.*, 1931, **49**, 3). The nitration product contained approximately equal amounts of the o- and p-*isomerides*; despite the fact that the *p*-compound is a solid a satisfactory separation cannot be readily achieved at this stage. Accordingly, the mixed nitro-acetates, after removal of any solid *p*-isomer by filtration, were hydrolysed directly with aqueous alcoholic hydrochloric acid. The hydrolysis product was readily separated, by fractional distillation, into o- and p-*nitrophenylmethylcarbinols*, which were then oxidised with chromic acid to the nitroacetophenones. In this way an overall yield of 21% of pure *p*-nitroacetophenone and 23% of *o*-nitroacetophenone of 80% purity was obtained without difficulty from phenylmethylcarbinol. von Braun and Bartsch (*Ber.*, 1913, **46**, 3053) have previously described the *p*-intermediates; the physical properties of their products were, however, very different from ours (thus the *p*-nitroacetate was described as an oil whereas we obtained it as a solid, m. p. 55—56°) and it seems almost certain that they were mixtures.

Some preliminary experiments on the nitration of α-phenylethyl chloride were also carried out; the α-chlorine atom was readily displaced with the formation, among other products, of α-(4-*nitrophenyl*)*ethyl nitrate*.

The second method (cf. Reich and Nicolaeva, *Helv. Chim. Acta*, 1919, **2**, 86) proceeds from ethylbenzene, thus:

$$\mathrm{Ph{\cdot}Et} \longrightarrow \underset{(o \text{ and } p)}{\mathrm{NO_2{\cdot}C_6H_4{\cdot}Et}} \longrightarrow \mathrm{NO_2{\cdot}C_6H_4{\cdot}C(:N{\cdot}OH){\cdot}Me} \longrightarrow \mathrm{NO_2{\cdot}C_6H_4{\cdot}CO{\cdot}Me}$$

Nitration of ethylbenzene yields a fairly easily separable mixture of *o*- and *p*-nitroethylbenzenes (Beilstein and Kuhlberg, *Annalen*, 1870, **156**, 206; Schultz and Flachsländer, *J. pr. Chem.*, 1902, **66**, 155; Cline and Reid, *J. Amer. Chem. Soc.*, 1927, **49**, 3150). The conversion of *o*-nitroethylbenzene into *o*-nitroacetophenone oxime with amyl nitrite and sodium ethoxide has been described in a patent (Höchst, D.R.-P. 109,663); in our hands the yields by this method were poor, but both *o*- and *p*-nitroethylbenzene were converted, in excellent yield, into the oximes by means of *tert.*-butyl nitrite and sodium *tert.*-butoxide. The oximes are readily hydrolysed by dilute sulphuric acid to the corresponding nitroacetophenones. By this route overall yields of 15% of pure *p*-nitroacetophenone and 20% of pure *o*-nitroacetophenone were obtained from ethylbenzene.

A number of other nitroacetophenone derivatives are described in the experimental section.

Experimental.

Nitration of Phenylmethylcarbinol.—Phenylmethylcarbinol (244 g.) was added, with periodic cooling, over 10 minutes to acetic anhydride (400 c.c.) containing sulphuric acid (2 c.c.). After being kept at room temperature for 15—30 minutes the acetic anhydride solution of phenylmethylcarbinyl acetate was stirred mechanically while fuming nitric acid (94 c.c.; *d* 1·50) was added dropwise over 1½—2 hours, the temperature being kept below 20° by ice-cooling. After being stirred for a further 1—2 hours at 15—20°, the product was poured into ice and water (1000 c.c.). Next day the mixture was filtered and the solid and filtrate treated separately.

Crystallisation of the solid (average yield 34 g.; 8%) from light petroleum (b. p. 40—60°) yielded α-(4-*nitrophenyl*)*ethyl acetate* in colourless prisms, m. p. 55—56° (Found: C, 57·7; H, 5·4; N, 6·8. $C_{10}H_{11}O_4N$ requires C, 57·4; H, 5·3; N, 6·7%).

The oily mixture of nitrophenylethyl acetates was separated from the filtrate and washed; it was not found possible to obtain an adequate separation of the isomers by fractional distillation. Accordingly the mixture was hydrolysed by refluxing for 6 hours with alcohol (1000 c.c.) and concentrated hydrochloric acid (200 c.c.); the residue obtained by evaporation on a water-bath under reduced pressure was then carefully fractionated using a 20 cm. Vigreux column. The progress of the fractionation was followed by observation of the refractive index, the following relations holding:

$$\%\ o\text{-isomer} = 9616(1{\cdot}5621 - n_D^{20});\quad n_D^{20} = n_D^{t} - 0{\cdot}00103(20 - t).$$

For the preparation of the nitroacetophenones it is most convenient to collect a first fraction, b. p. 125—140°/2 mm., containing (mean of 4 runs) 86% of *o*-nitrophenylmethylcarbinol (average yield 108 g.; 32%), a middle fraction, b. p. 140—145°/2 mm. (49% of *o*-isomer; average yield 27 g. = 8%), and an end fraction, b. p. 145—155°/2 mm. (88% *p*-isomer; average yield 75·5 g. = 23%); the pure isomers can be obtained by further fractionation of the head and tail fractions.

Pure o-*nitrophenylmethylcarbinol* so prepared was a viscous yellow oil with a marked sweet taste, b. p. 131—132°/3 mm., 124—126°/1·5 mm., n_D^{20} 1·5517 (Found: C, 56·8; H, 5·7; N, 8·35. $C_8H_9O_3N$ requires C, 57·5; H, 5·4; N, 8·4%); the p-*nitrobenzoate* crystallised from alcohol in pale yellow needles, m. p. 145—146° (Found: C, 56·9; H, 3·95. $C_{15}H_{12}O_6N_2$ requires C, 57·0; H, 3·8%).

Pure p-*nitrophenylmethylcarbinol*, obtained by hydrolysis of the crystalline acetate, was a sweet-tasting viscous yellow oil, b. p. 161—163°/4 mm., n_D^{20} 1·5621 (Found: C, 56·8; H, 5·4; N, 8·6%); the p-*nitrobenzoate* crystallised from alcohol in colourless leaflets, m. p. 138° (Found: C, 56·95; H, 3·9%).

Oxidation of Nitrophenylmethylcarbinols.—(a) o-*Nitroacetophenone*. *o*-Nitrophenylmethylcarbinol (86%; 108 g.) was added during 10 minutes to a stirred solution of sodium dichromate (190 g.) in water (475 c.c.) and sulphuric acid (95 c.c.), previously heated to 60°. After the internal temperature, which rose to 95°, had again fallen to 60° (about 15 minutes) the mixture was stirred at 60° for a further 3 hours and then poured into ice and water (1000 c.c.). The product was extracted with benzene and the extract washed with 10% sodium carbonate solution, dried, and distilled, *o*-nitroacetophenone being collected at 134—135°/4 mm., 146—148°/7 mm. The composition of the product can be determined by measurement of the refractive index; the following relations hold:

$$\%\ o\text{-isomer} = 5181(1{\cdot}5497 - n_D^{20});\quad n_D^{20} = n_D^{t} - 0{\cdot}00055(20 - t).$$

The average yield of *o*-nitroacetophenone from three such runs was 92 g. (85%); the product contained 80% of the *o*-isomer.

(b) p-*Nitroacetophenone*. *p*-Nitrophenylmethylcarbinol (87%; 69 g.) was oxidised as described for the *o*-isomer; the solid product (62·6 g.) was crystallised from methanol, yielding 44·5 g. (65%) of pure *p*-nitroacetophenone, m. p. 79—80°.

Nitration of α-Phenylethyl Chloride.—α-Phenylethyl chloride (40 g.; Norris, Watt, and Thomas, *J. Amer. Chem. Soc.*,

1916, **38**, 1078) was added dropwise with mechanical stirring over 5 hours to fuming nitric acid (200 c.c.; *d* 1·50), the temperature being kept below −10°; chlorine was freely evolved during the later part of the process. The product was poured into water and the resulting paste filtered off and pressed well. Crystallisation of the solid (25·7 g.; 45%) from alcohol yielded *α-(4-nitrophenyl)ethyl nitrate* in almost colourless rectangular leaflets, m. p. 50° (Found: C, 45·9; H, 4·0; N, 13·2. $C_8H_8O_5N_2$ requires C, 45·3; H, 3·8; N, 13·2%); the position of the nuclear nitro-group was established by oxidation to *p*-nitrobenzoic acid.

Nitration of Ethylbenzene (cf. Cline and Reid, *J. Amer. Chem. Soc.*, 1927, **49**, 3150).—Ethylbenzene (867 g.) was treated with stirring with a mixture of nitric (436 c.c.; *d* 1·459) and sulphuric (436 c.c.; *d* 1·84) acids, the temperature being kept at 25—30° by external cooling; the reaction mixture was then heated on the water-bath for 2 hours. The nitration product was separated from the cooled mixture, washed with sodium carbonate, dried, and fractionally distilled under reduced pressure through a long column. The course of the fractionation was followed by observation of the refractive index, the following relations holding:

$$\%\ o\text{-isomer} = 14080(1{\cdot}5459 - n_D^{15});\quad n_D^{15} = n_D^t - 0{\cdot}00052(15 - t).$$

Two fractionations gave 485 g. (39%) of *o*-nitroethylbenzene, b. p. 87—89°/4 mm., n_D^{15} 1·5388, 130 g. of an intermediate mixture, and 471 g. (38%) of *p*-nitroethylbenzene, b. p. 102—104°/4 mm., n_D^{15} 1·5459. The distillation residue yielded 7 g. of 2 : 4-dinitroethylbenzene, b. p. 148—150°/8 mm.

Oximation of Nitroethylbenzene.—Sodium *tert.*-butoxide was prepared by dissolving sodium wire (25 g.) in dry *tert.*-butyl alcohol (1000 c.c.) on the water-bath and distilling off 300 c.c. of butyl alcohol after the reaction was complete; the product was cooled to room temperature and treated with a mixture of *o*-nitroethylbenzene (151 g.) and *tert.*-butyl nitrite (110 g.; b. p. 65—66°; prepared in 62% yield by the method described for *n*-butyl nitrite by Noyes, *Org. Synth.*, 1936, **16**, 7). After being kept overnight the mixture was heated to 50° on the water-bath and then steam-distilled to remove *tert.*-butyl alcohol; the steam distillate consists largely of a constant-boiling mixture of water and the alcohol and can be used for the preparation of more nitrite. The residue from the steam distillation was cooled and extracted with chloroform; the chloroform extract was shaken with 10% sodium hydroxide. This alkaline washing was added to the aqueous layer from the chloroform extraction and the whole treated with carbon dioxide until precipitation was complete. The precipitated oxime was filtered off and dried in a vacuum desiccator; m. p. 113—114°, yield 80 g. (73·5% allowing for 91 g. of redistilled *o*-nitroethylbenzene obtained by distillation of the washed chloroform extract); *o*-nitroacetophenone oxime recrystallised from methanol had m. p. 117° (Höchst, D.R.P. 109,663, give m. p. 115°).

p-Nitroacetophenone oxime, m. p. 174° after crystallisation from methanol (Posner, *Annalen*, 1912, **389**, 42, gives m. p. 172—173°), was similarly obtained in 67% yield from *p*-nitroethylbenzene. The reaction does not proceed so smoothly with 2 : 4-dinitroethylbenzene which gives only 27% of 2 : 4-dinitroacetophenone oxime, m. p. 121° from 90% alcohol (Reich and Nicolaeva, *Helv. Chim. Acta*, 1919, **2**, 86, give m. p. 124°).

Hydrolysis of Oximes.—Crude *o*-nitroacetophenone oxime (76 g.), water (100 c.c.), and sulphuric acid (50 c.c.) were refluxed, with stirring, for 3 hours. The cooled reaction product was extracted with chloroform, washed with dilute sodium hydroxide solution, dried, and distilled, yielding 50 g. (72%) of pure *o*-nitroacetophenone, b. p. 129°/3 mm., m. p. 23°; 9 g. of unreacted oxime were recovered from the alkali washings.

p-Nitroacetophenone oxime was similarly hydrolysed in 60% yield to *p*-nitroacetophenone, b. p. 138°/1·5 mm., m. p. 80° from methanol (Drewsen, *Annalen*, 1882, **212**, 60, gives m. p. 80—81°), and 2 : 4-dinitroacetophenone oxime in 30% yield to 2 : 4-*dinitroacetophenone*, b. p. 192°/7 mm., m. p. 41—42° from methanol (Found: C, 45·7; H, 2·9. $C_8H_6O_5N_2$ requires C, 45·7; H, 2·9%).

Bromination of 2 : 4-dinitroacetophenone (2·5 g.) in acetic acid with bromine (1·6 g.) gave *ω-bromo-2 : 4-dinitroacetophenone*, m. p. 90—91° after crystallisation from methanol (Found: C, 33·6; H, 1·7. $C_8H_5O_5N_2Br$ requires C, 33·25; H, 1·7%).

Derivatives of o-Nitroacetophenone.—*o*-Nitroacetophenone, prepared by the acetoacetic ester synthesis from *o*-nitrobenzoyl chloride, solidified on keeping at −70° for some hours. The crystalline product, m. p. 24·5°, was used for the preparation of the following derivatives.

The oxime, prepared in pyridine and twice crystallised from aqueous alcohol, had m. p. 117°. The *semicarbazone* crystallises from dilute acetic acid, m. p. 208—210° (Found: C, 49·0; H, 5·0; N, 25·2. $C_9H_{10}O_3N_4$ requires C, 48·6; H, 4·5; N, 25·2%), and the 2 : 4-*dinitrophenylhydrazone* from glacial acetic acid, m. p. 168—170° (Found: C, 49·0; H, 3·3. $C_{14}H_{11}O_8N_5$ requires C, 48·8; H, 3·2%).

All analyses were micro-analyses carried out by Mr. G. Ingram.

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CHEMICAL DEFENCE EXPERIMENTAL STATION, PORTON, NR. SALISBURY. [*Received, January 19th*, 1946.]

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141. *New Potential Chemotherapeutic Agents. Part V. Basically-substituted* iso*Alloxazines.*

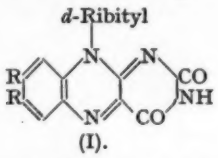
By F. E. KING and R. M. ACHESON.

A series of *iso*alloxazines modelled on riboflavin, but with the ribityl side-chain replaced by diethylaminoalkyl groups and methyl, chloro, and methoxyl substituents at the 6-position, has been synthesised from alloxan and the appropriate *o*-phenylenediamines. The products, isolated as *monohydrochlorides*, exhibit in solution the intense fluorescence characteristic of this class of compound.

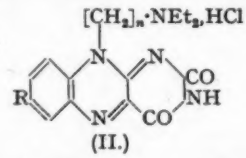
ACCORDING to Fildes, McIlwain, Woods, and others (for references see Hinshelwood, *Ann. Reports*, 1944, **41**, 25), the inhibitory action of many chemotherapeutic agents on the metabolism of bacteria, and probably of other micro-organisms, *e.g.*, protozoa, is due to their interference with the utilisation of growth factors to which they bear a close structural resemblance. It is believed that by virtue of this similarity of structure antibiotic substances are able to compete with the normal metabolites for their specific enzymes, and considerable evidence now exists to show that it is often the oxidation–reduction enzymes which are thus inhibited.

Among the factors necessary for bacterial growth is riboflavin (I, R = Me), a constituent of several widely occurring enzymes. Two examples have lately been recorded of bacterial inhibition by riboflavin analogues,

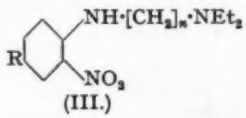
i.e., 6 : 7-dichloro-9-*d*-ribityl*iso*alloxazine (I; R = Cl) (Kuhn, Weygand, and Möller, *Ber.*, 1943, **76**, 1044) and 2 : 4-diamino-6 : 7-dimethyl-9-*d*-ribityldihydrophenazine (Woolley, *J. Biol. Chem.*, 1944, **154**, 31), both of which



(I).



(II.)



(III.)

are antagonised by riboflavin, and Madinaveitia (*Biochem. J.*, 1944, **38**, xxvii) has reported that the antibacterial activity of certain antimalarial drugs is also reversed by the vitamin.

The experiments now to be described, which were begun in June, 1944, are part of a more comprehensive undertaking to provide a series of synthetical variants of the riboflavin molecule for examination both as potential antimalarials and as general bacteriostatic agents. Since many of the most successful cell inhibitors are basically-substituted, the modification initially contemplated in the riboflavin molecule was the replacement of the 9-ribityl substituent by basic side-chains, for example, the dialkylaminoalkyl groups typical of the current antimalarial drugs, combined with variations in the substituents of the aromatic nucleus. In view of the recent communication of Hall and Turner (*J.*, 1945, 699) describing their attempts to prepare precisely similar derivatives *e.g.*, (II; R = H, *n* = 3), we present this account of our experiments.

The basically-substituted *iso*alloxazines (II) were obtained by the standard method of synthesis, *viz.*, condensation of the *o*-phenylenediamines derived by catalytic reduction of 4-substituted-2-nitroalkylanilines (III) with alloxan, generally in hot 85—90% ethanolic hydrogen chloride. In this way were obtained 9-β-diethylaminoethyl*iso*alloxazine, and the 6-methyl-, 6-chloro- and 6-methoxy- derivatives of both 9-β-diethylaminoethyl- and 9-γ-diethylamino-*n*-propyl-*iso*alloxazine, all of which separated in satisfactory yields from their reaction mixtures as highly crystalline hydrated *monohydrochlorides*. Condensation in boric–acetic acid solution (Kuhn and Weygand, *Ber.*, 1935, **68**, 1282) was tried in one case, but was less successful owing to the difficulty of removing boric acid from the product. The amine hydrochlorides are very freely soluble in water giving yellow to orange-yellow solutions with a brilliant green fluorescence. The *iso*alloxazine bases are also highly water-soluble, but crystalline *picrates* were precipitated on the addition of sodium picrate to aqueous solutions of the hydrochlorides.

The synthesis of the necessary nitroamines (III) was effected either from sodium salts of the *N*-acylated nitroanilines by alkylation with diethylaminoalkyl chlorides followed by acid hydrolysis of the acyl group, or by the condensation of *o*-chloronitrobenzenes with diethylaminoalkylamines. Thus, the action of cold 90% sulphuric acid on 2-nitro-*p*-toluenesulphon-(β-diethylaminoethyl)anilide gave (III; R = H, *n* = 2), an intermediate for the amine (II; R = H, *n* = 2), and a similar process was applied to the synthesis from their *p*-toluenesulphonamides of the compounds (III; R = OMe, *n* = 2) and (III; R = OMe, *n* = 3). The amine (III; R = OMe, *n* = 2) was also obtained by the action of hot hydrochloric acid on its *acetyl* derivative, for which 3-nitro-4-acetamidoanisole was condensed with β-chloroethyldiethylamine in presence of sodamide (cf. Eisleb, *Ber.*, 1941, **74**, 1433). The same alkylation technique was also used for the synthesis of the 4-methyl compound (III; R = Me, *n* = 2) and of its analogue (III; R = Cl, *n* = 2), but these and the remaining nitroamines (III; R = Me, *n* = 3) and (III; R = Cl, *n* = 3) were more conveniently prepared by the second general method, *i.e.*, heating the *o*-chloronitrobenzenes with β-diethylaminoethyl- or γ-diethylamino-*n*-propylamine and sodium acetate. The yields of β-diethylaminoethylamine from the catalytic reduction of diethylaminomethyl cyanide have been considerably improved by a slight elaboration of the recorded procedure (cf. Winans and Adkins, *J. Amer. Chem. Soc.*, 1933, **55**, 4167).

From chloro-2 : 4-dinitrobenzene and γ-diethylamino-*n*-propylamine, 2 : 4-*dinitro-γ-diethylamino*-n-*propylaniline* has been prepared, but its reduction and condensation with alloxan have failed to give the expected 6-amino*iso*alloxazine. Experiments on the preparation of these amino derivatives are continuing.

The results of biological tests on some of the foregoing *iso*alloxazines will be published in due course.

Experimental.

2-Nitro-β-diethylaminoethylaniline (III; R = H, *n* = 2).—A mixture of β-chloroethyldiethylamine hydrochloride (43 g.) and 2-nitro-*p*-toluenesulphonanilide (58 g.) (Usherwood and Whiteley, *J.*, 1923, **123**, 1084) dissolved in alcohol (300 c.c.) with an alcoholic solution of sodium (11·5 g. in 250 c.c.) was heated under reflux for 36 hours on a steam-bath. The product obtained by evaporation of the filtered liquid was shaken with water (150 c.c.) and concentrated hydrochloric acid (50 c.c.), and, after removal of unchanged 2-nitro-*p*-toluenesulphonanilide, the solution was treated with aqueous sodium hydroxide (50%) and extracted with chloroform. 2-Nitro-*p*-toluenesulphon-(β-diethylaminoethyl)anilide was thus obtained as a pale brown syrup (75 g.) and identified by the *picrate*, which crystallised from ethanol–acetone in lemon-yellow flat prisms, m. p. 152—154° (Found: C, 47·9; H, 4·4; N, 13·2. $C_{19}H_{25}O_4N_3S,C_6H_3O_7N_3$ requires C, 48·4; H, 4·5; N, 13·5%).

Ice-cold sulphuric acid (250 c.c. of 90%) was cautiously added to the above sulphonanilide (74 g.) and the mixture left for 12 hours at room temperature. The resulting solution was then slowly poured into a mixture of ice and excess of aqueous ammonia and the liberated base collected in ether and distilled. The pure *nitroamine* (37 g.) was a bright red oil, b. p. 164—166°/0·05 mm. (Found: C, 61·1; H, 7·8; N, 17·2. $C_{12}H_{19}O_2N_3$ requires C, 60·7; H, 8·0; N, 17·7%), and formed a *picrate* which separated from alcohol–acetone in orange-yellow rods, m. p. 158° (Found: C, 46·4; H, 5·0. $C_{12}H_{19}O_2N_3,C_6H_3O_7N_3$ requires C, 46·4; H, 4·7%).

*9-β-Diethylaminoethyliso*alloxazine *Hydrochloride* (II; R = H, *n* = 2).—The nitroamine (III; R = H, *n* = 2)

(10 g.) was dissolved in ethanol (100 c.c.) and reduced over Raney nickel at room temperature with hydrogen at 50 atm. The resulting triamine was not isolated, but after filtration the almost colourless liquid was immediately acidified with concentrated hydrochloric acid (12·5 c.c., 3 mols.) diluted with a little alcohol, and heated on a steam-bath with a solution of alloxan monohydrate (6·8 g., 1 mol.) in water (7—8 c.c.). Within a few minutes a chrome-yellow crystalline precipitate appeared which was collected after the solution had cooled to room temperature. The product (7·5 g.) readily dissolved in water to a bright yellow solution with a brilliant yellow-green fluorescence, and was most conveniently recrystallised by the addition of a small amount of water to a suspension of the solid in boiling ethanol. *9-Diethylaminoethyl*iso*alloxazine hydrochloride* separated on cooling as glittering yellow rectangular plates, m. p. 282—283° (decomp.) (Found on a specimen dried at 100° in a high vacuum: C, 55·1; H, 5·8; N, 21·1; Cl, 9·6. $C_{16}H_{19}O_2N_5,HCl$ requires C, 54·9; H, 5·8; N, 20·0; Cl, 10·2%). Mixing aqueous solutions of the hydrochloride and of sodium picrate precipitated the *picrate*, which crystallised from ethanol–water in yellow-green prisms, m. p. 226° (decomp.) (Found: C, 49·0; H. 4·2; N, 20·5. $C_{16}H_{19}O_2N_5,C_6H_3O_7N_3$ requires C, 48·7; H, 4·1; N, 20·7%).

β-Diethylaminoethylamine (cf. Winans and Adkins, *loc. cit.*).—A mixture of diethylaminomethyl cyanide (20 g.) (Luten, *J. Org. Chem.*, 1939, **3**, 588) and Raney nickel in a high-pressure hydrogenator was cooled to −30°, and a solution of liquid ammonia (20 c.c.) in ether (50 c.c.) added. The apparatus was then filled with hydrogen at 96 atm. and rapidly heated (15—20 minutes) to 140°. When cold, the contents were slowly brought to room pressure and filtered from catalyst, and the product and ether washings fractionated. No high-boiling by-products were formed, and the β-diethylaminoethylamine (12·8 g., 61·5%) of b. p. 144—150° was characterised as the dipicrate, m. p. 211° (decomp.) (Found: C, 37·7; H, 3·9. Calc. for $C_6H_{16}N_2,2C_6H_3O_7N_3$: C, 37·7; H, 3·8%).

3-Nitro-p-N-(*β-diethylaminoethyl*)*toluidine*, (III; R = Me, *n* = 2).—(i) 4-Chloro-3-nitrotoluene (4·11 g., 1 mol.) and β-diethylaminoethylamine (3·1 g., 1·1 mol.) mixed with anhydrous sodium acetate (5·0 g.) were heated in an oil-bath rising from 100° to 140° during 7 hours. The cooled product was shaken with dilute hydrochloric acid, unchanged chloronitrotoluene extracted with ether, and after addition of sodium hydroxide the liberated *3-nitro*-p-N-(*β-diethylaminoethyl*)*toluidine* isolated as a deep-red oil (1·8 g.), b. p. 125—135°/0·033 mm. (Found: C, 62·4; H, 8·3; N, 17·6. $C_{13}H_{21}O_2N_3$ requires C, 62·2; H, 8·4; N, 16·7%). The *picrate* formed minute yellow needles from alcohol–benzene, m. p. 176° (Found: C, 47·5; H, 5·0; N, 18·1. $C_{13}H_{21}O_2N_3,C_6H_3O_7N_3$ requires C, 47·5; H, 5·0; N, 17·5%).

(ii) To a solution of 3-nitroacet-*p*-toluidide (5·5 g.) and β-chloroethyldiethylamine (4·25 g., 1·1 mol.) in dry toluene (50 c.c.), powdered sodamide (1·1 g., 1·1 mol.) was added during 15 minutes (cf. Eisleb, *loc. cit.*). The mixture, vigorously stirred, was slowly heated to 100° (1 hour), and after 3 hours at 100° was heated to boiling for a further 1 hour. The filtered solution was extracted with hydrochloric acid (5%), and from the aqueous extract, by shaking with sodium hydroxide and ether, the *acetyl* derivative of (III; R = Me, *n* = 2) was obtained as a yellow-red oil (4·1 g., 49·4%), b. p. 170—180°/0·33 mm. (Found: C, 61·2; H, 8·0; N, 14·7. $C_{15}H_{23}O_3N_3$ requires C, 61·4; H, 7·9; N, 14·3%), characterised by its *picrate* which separated from aqueous ethanol in yellow prisms, m. p. 119° (Found: C, 48·1; H, 4·9. $C_{15}H_{23}O_3N_3,C_6H_3O_7N_3$ requires C, 48·2; H, 5·0%). Hydrolysis of the acetyl compound (4·1 g.) with concentrated hydrochloric acid (25 c.c.) for 4—5 hours on a steam-bath gave 3-nitro-*p-N*-(β-diethylaminoethyl)toluidine, b. p. 150—160°/0·4 mm., which was identified by its picrate, m. p. and mixed m. p. 176°.

*6-Methyl-9-β-diethylaminoethyl*iso*alloxazine Hydrochloride*, (II; R = Me, *n* = 2).—The nitroamine (III; R = Me, *n* = 2) (2·66 g.) was hydrogenated in methanol (30 c.c.) over Raney nickel at room temperature and 2 atm. The colourless solution was filtered into concentrated hydrochloric acid (3·0 c.c., 3 mols.), a hot saturated aqueous solution of alloxan hydrate (1·87 g., 1·1 mol.) added, and the mixture gently heated under reflux for 45 minutes. The dark fluorescent solution was evaporated under diminished pressure, and the residue dissolved in boiling ethanol (10 c.c.). Acetone was added, crystallisation initiated by seeding, and next day the product (2·32 g., 62%), m. p. 220°, was collected. Repeated crystallisation from aqueous ethanol gave the *iso*alloxazine *hydrochloride trihydrate* as minute yellow plates, m. p. 259° (decomp.) (Found: C, 48·7; H, 6·6; N, 17·2; Cl, 8·5. $C_{17}H_{21}O_2N_5,HCl,3H_2O$ requires C, 48·9; H, 6·7; N, 16·8; Cl, 8·5%. Found after drying in a high vacuum at 120°: C, 55·4; H, 6·1; N, 19·0; Cl, 9·8. $C_{17}H_{21}O_2N_5,HCl$ requires C, 56·1; H, 6·1; N, 19·3; Cl, 9·8%). The *picrate*—yellow-orange prisms from aqueous ethanol—had m. p. 225—227° (decomp.) (Found: C, 47·9; H, 4·6; N, 19·3. $C_{17}H_{21}O_2N_5,C_6H_3O_7N_3,H_2O$ requires C, 48·1; H, 4·5; N, 19·5%).

When the nitroamine (III; R = Me, *n* = 2) (2·37 g.) dissolved in acetic acid (30 c.c.) was hydrogenated at room temperature and 2 atm. over palladised charcoal, and the colourless filtrate added to hot acetic acid (60 c.c.) containing alloxan hydrate (1·9 g.) and boric acid (2 g.), condensation occurred rapidly. After 30 minutes at 30°, the solution was evaporated to dryness under reduced pressure, and the residue triturated at 5° with water (10 c.c.) and concentrated hydrochloric acid (1 c.c., *ca.* 1·05 mol.). The product obtained on filtration from boric acid and evaporation to dryness was dissolved in alcohol, and the filtered solution seeded and left till next day. Recrystallisation of the yellow precipitate (1·07 g., 31·2%), m. p. *ca.* 246° (decomp.), from alcohol–water gave the pure *iso*alloxazine hydrochloride as yellow plates, m. p. 259° (decomp.) (Found after drying at 120° in a vacuum: C, 55·6; H, 6·4; Cl, 9·6%).

3-Nitro-p-N-(*γ-diethylamino*-n-*propyl*)*toluidine* (III; R = Me, *n* = 3).—From the product obtained by heating γ-diethylamino-*n*-propylamine (5 g.), 4-chloro-3-nitrotoluene (8 g.), and anhydrous sodium acetate (10 g.) at 100° rising to 140° during 5 hours, unchanged chloronitrotoluene was removed by shaking with dilute hydrochloric acid and ether. From the aqueous solution *3-nitro*-p-N-(*γ-diethylamino*-n-*propyl*)*toluidine* was precipitated by alkali as a thick orange-red oil, b. p. 145—155°/0·1 mm. (Found: C, 63·3; H, 8·8. $C_{14}H_{23}O_2N_3$ requires C, 63·4; H, 8·7%), characterised by its *picrate* which crystallised as yellow-red plates, m. p. 155·5°, from aqueous ethanol (Found: C, 48·4; H, 5·0; N, 16·4. $C_{14}H_{23}O_2N_3,C_6H_3O_7N_3$ requires C, 48·6; H, 5·3; N, 17·0%).

6-Methyl-9-γ-diethylamino-n-*propyl*iso*alloxazine Hydrochloride* (II; R = Me, *n* = 3).—A methanol solution (40 c.c.) of the amine (III; R = Me, *n* = 3) (4 g.) hydrogenated over Raney nickel at room temperature and 2 atm. was rapidly filtered into concentrated hydrochloric acid (8 c.c.) and mixed with a hot saturated aqueous solution of alloxan hydrate (2·6 g.). After several minutes on a steam-bath, the solution was concentrated under reduced pressure and the *iso*alloxazine *hydrochloride* precipitated with acetone as a dark brown powder (3·07 g., 48·8%), m. p. 270° (decomp.). Repeated crystallisation from aqueous ethanol gave the dihydrate as yellow-red plates, m. p. 286° (decomp.) (Found: C, 52·6; H, 6·7; N, 17·0; Cl, 9·1. $C_{19}H_{23}O_2N_5,HCl,2H_2O$ requires C, 52·3; H, 6·8; N, 16·9; Cl, 8·6%. Found on drying in a vacuum at 100°: loss 3·3; C, 54·4; H, 6·7; N, 17·1. $C_{19}H_{23}O_2N_5,HCl,H_2O$ requires loss 4·4; C, 54·6; H, 6·6; N, 17·7%. Found on drying in a vacuum at 120°: loss 7·4; C, 56·9; H, 6·6. $C_{19}H_{23}O_2N_5,HCl$ requires loss 8·7; C, 57·2; H, 6·4%). The *picrate* separated from aqueous ethanol, in red prisms, m. p. 258—260° (decomp.) (Found: C, 50·5; H, 4·6; N, 19·1. $C_{19}H_{23}O_2N_5,C_6H_3O_7N_3$ requires C, 50·5; H, 4·6; N, 19·6%).

4-Chloro-2-nitro-N-(*β-diethylaminoethyl*)*aniline* (III; R = Cl, *n* = 2).—4-Chloro-2-nitroacetanilide (8·75 g., 1 mol.), β-chloroethyldiethylamine (5·95 g., 1·1 mol.), and sodamide (1·72 g.) were condensed in toluene solution (100 c.c.) as already described for the compound (III; R = Me, *n* = 2). The resulting *4-chloro-2-nitroacet*-N-(*β-diethylaminoethyl*)*anilide* (8·2 g., 67·5%) was a yellow oil, b. p. 170°/0·35 mm. (Found: C, 53·9; H, 6·3; N, 12·8; Cl, 11·5. $C_{14}H_{20}O_3N_3Cl$ requires C, 53·6; H, 6·4; N, 13·4; Cl, 11·3%), and was characterised as a *picrate* crystallising from aqueous ethanol in yellow prisms, m. p. 144° (Found: C, 44·1; H, 4·2; Cl, 6·9. $C_{14}H_{20}O_3N_3Cl,C_6H_3O_7N_3$ requires C, 44·2; H, 4·2; Cl, 6·5%).

(i) The above acetylated amine (7·1 g.) was heated on a steam-bath for 4—5 hours with concentrated hydrochloric acid (25 c.c.), and the deep red solution basified and extracted with ether. Distillation gave 4-*chloro*-2-*nitro*-N-(β-*diethylaminoethyl*)*aniline* (5·45 g., 88·6%), b. p. 158—163°/0·4 mm., which afterwards crystallised in dark red prisms, m. p. 53—54° (Found: C, 53·4; H, 6·6; N, 14·9; Cl, 13·4. $C_{12}H_{18}O_2N_3Cl$ requires C, 53·1; H, 6·6; N, 15·5; Cl, 13·1%). The *picrate* crystallised from aqueous ethanol in minute yellow plates, m. p. 204° (Found: C, 43·2; H, 4·4; N, 16·9; Cl, 7·2. $C_{12}H_{18}O_2N_3Cl,C_6H_3O_7N_3$ requires C, 43·2; H, 4·2; N, 16·8; Cl, 7·1%). The *picrolonate*, orange-yellow plates from aqueous ethanol, had m. p. 205° (decomp.) (Found: C, 49·4; H, 4·7; Cl, 6·6. $C_{12}H_{18}O_2N_3Cl,C_{10}H_8O_5N_4$ requires C, 49·2; H, 5·0; Cl, 6·6%).

(ii) A mixture of 2 : 5-dichloronitrobenzene (8·6 g.), β-diethylaminoethylamine (3·06 g.), and anhydrous sodium acetate (7 g.), heated at 100—135° for 5 hours, on working up gave the amine (III; R = Cl, *n* = 2) (3·63 g., 50·4%), m. p. 52° undepressed on mixing with a specimen prepared by method (i).

6-*Chloro*-9-β-*diethylaminoethyl*iso*alloxazine Hydrochloride* (II; R = Cl, *n* = 2).—The alkylated chloronitroaniline (4·08 g.) was reduced in methanol (40 c.c.) over Raney nickel at room temperature and 2 atm., and the resulting colourless solution filtered and heated on a steam-bath with concentrated hydrochloric acid (4·6 c.c., 3 mols.) and saturated aqueous alloxan (2·66 g.) for 30 minutes. The sticky product obtained on evaporation, dissolved in alcohol (15 c.c.) and precipitated with dry acetone, gave on washing with ethanol a yellow-green solid (2·46 g., 42·5%), m. p. 243° (decomp.). By repeated crystallisation from ethanol–water, the *iso*alloxazine *hydrochloride* was obtained as a *monohydrate* in scintillating yellow-brown needles, m. p. 252—253° (decomp.) (Found: C, 47·9; H, 5·5; N, 16·9; Cl, 18·1. $C_{16}H_{18}O_2N_5Cl,HCl,H_2O$ requires C, 47·7; H, 5·2; N, 17·4; Cl, 17·6%. Found on a specimen vacuum dried at 120°: C, 49·9; H, 4·9; N, 18·0; Cl, 18·9. $C_{16}H_{18}O_2N_5Cl,HCl$ requires C, 50·0; H, 4·9; N, 18·2; Cl, 18·5%). The *picrate* was obtained as yellow prisms, m. p. 241—243° (decomp.), from ethanol–water (Found: C, 45·7; H, 3·7; Cl, 6·6. $C_{16}H_{18}O_2N_5Cl,C_6H_3O_7N_3$ requires C, 45·8; H, 3·6; Cl, 6·6%).

4-*Chloro*-2-*nitro*-N-(γ-*diethylamino*-n-*propyl*)*aniline* (III, R = Cl; *n* = 3).—γ-Diethylamino-*n*-propylamine (3·9 g.), 2 : 5-dichloronitrobenzene (8·6 g.) and anhydrous sodium acetate (7 g.) were heated from 100° to 140° during 3 hours, and the product was worked up in the usual way. The *amine* (III; R = Cl, *n* = 3) (5·7 g.), a thick orange-red oil, b. p. 164—165°/0·33 mm., crystallised in large prisms, m. p. 38° (Found: C, 54·6; H, 7·0. $C_{13}H_{20}O_2N_3Cl$ requires C, 54·6; H, 7·0%), and was characterised by a *picrate* which separated from ethanol–water in orange-red plates, m. p. 168·5° (Found: C, 44·4; H, 4·9; N, 15·8; Cl, 7·1. $C_{13}H_{20}O_2N_3Cl,C_6H_3O_7N_3$ requires C, 44·4; H, 4·5; N, 16·3; Cl, 6·9%).

6-*Chloro*-9-γ-*diethylamino*-n-*propyl*iso*alloxazine Hydrochloride* (II; R = Cl, *n* = 3).—The colourless solution obtained by hydrogenation of the nitroamine (III; R = Cl, *n* = 3) (4 g.) in methanol (40 c.c.) over Raney nickel was heated with concentrated hydrochloric acid (8 c.c.) and alloxan hydrate (2·35 g.) in hot water (4 c.c.) on a steam-bath for 30 minutes. Evaporation left a dark oil which when crystallised from alcohol gave a brown powder (2·8 g., 49·1%), m. p. 282° (decomp.). Recrystallisation from ethanol–water afforded the *iso*alloxazine *hydrochloride monohydrate* as yellow plates, m. p. 285—286° (decomp.) (Found: C, 49·1; H, 5·4; N, 16·7; Cl, 16·9. $C_{17}H_{20}O_2N_5Cl,HCl,H_2O$ requires C, 49·0; H, 5·5; N, 16·8; Cl, 17·1%. Found after drying in a vacuum at 100°: loss, 2·1; C, 50·0; H, 5·4; N, 17·3; Cl, 18·0. $C_{17}H_{20}O_2N_5Cl,HCl,\frac{1}{2}H_2O$ requires loss 2·2; C, 50·1; H, 5·4; N, 17·2; Cl, 17·4%). The *picrate* crystallised from ethanol–water in light brown prisms, m. p. 263° (decomp.) (Found: C, 46·6; H, 4·1; N, 18·3; Cl, 6·3. $C_{17}H_{20}O_2N_5Cl,C_6H_3O_7N_3$ requires C, 46·7; H, 3·9; N, 19·0; Cl, 6·0%).

3-*Nitro*-4-β-*diethylaminoethylaminoanisole* (III; R = OMe, *n* = 2) (cf. King, Beer, and Waley, this vol., p. 92).—3-Nitro-4-acetamidoanisole (10·5 g.) and β-chloroethyldiethylamine (7·5 g., 1·1 mol.) were condensed in the usual way by means of sodamide (2·2 g., 1·1 mol.) in toluene to give a brown oil (13·5 g.), identified as 3-nitro-4-acet-(β-diethylaminoethyl)-amidoanisole by its *picrate*, which crystallised from ethanol in yellow rhombic tablets, m. p. 156—157° (Found: C, 47·1; H, 4·6. $C_{15}H_{23}O_4N_3,C_6H_3O_7N_3$ requires C, 46·8; H, 4·8%). Hydrolysis of the acetamido compound with boiling concentrated hydrochloric acid for 1 hour, followed by evaporation at 60° and the addition of alkali, gave 3-nitro-4-β-diethylaminoethylaminoanisole, shown by its picrate, m. p. 181°, to be identical with the base already obtained through the *p*-toluenesulphonamide (*loc. cit.*).

6-*Methoxy*-9-β-*diethylaminoethyl*iso*alloxazine Hydrochloride* (II; R = OMe, *n* = 2).—The alkylated nitroanisidine (8·2 g.) dissolved in ethanol (50 c.c.) and acidified with concentrated hydrochloric acid (9 c.c., 3 mol.) was reduced at 2—3 atm. in presence of palladised charcoal. The colourless solution filtered from catalyst, together with alcohol washings (40 c.c.), was added to a solution of alloxan hydrate (4·8 g.) in hot water (5 c.c.) and the mixture heated on a steam-bath for 2—3 minutes. The orange-brown crystalline solid (6·5—7 g.), m. p. 235—238° (decomp.), which separated on cooling was collected and washed with ethanol. It was best crystallised from a little water, though with very considerable loss; dilution with alcohol, in which the *iso*alloxazine is very sparingly soluble, did not produce any rapid further precipitation, and lengthy contact with the solution appeared to result in some decomposition. The recrystallised salt, minute orange needles, m. p. 247° (decomp.), was evidently a hydrated monohydrochloride (Found: Cl, 7·7%); it was characterised as a *picrate* which crystallised from water in feathery red plates, m. p. 182° (decomp., rapid heating) (Found: C, 44·4; H, 4·8; N, 17·7. $C_{17}H_{21}O_3N_5,C_6H_3O_7N_3,3H_2O$ requires C, 44·1; H, 4·8; N, 17·9%. Found after drying at 100°: loss, 3·0; C, 44·9; H, 4·8; N, 18·1. $C_{17}H_{21}O_3N_5,C_6H_3O_7N_3,2H_2O$ requires loss, 3·0; C, 45·4; H, 4·6; N, 18·4%).

3-*Nitro*-4-γ-*diethylamino*-n-*propylaminoanisole* (III; R = OMe, *n* = 3).—A solution of sodium (5·7 g.) in alcohol (400 c.c.) containing 3-nitro-4-*p*-toluenesulphonamidoanisole (36 g.) and γ-chloro-*n*-propyldiethylamine hydrochloride (25 g.) was heated under reflux for 36 hours. After removal of sodium chloride and alcohol, the unreacted sulphonamide was extracted from a solution of the product in ether by aqueous sodium hydroxide, and the dried ethereal solution evaporated. On being kept, the pale orange oil solidified to crystalline 3-nitro-4-*p*-toluenesulphon-(γ-diethylamino-*n*-propyl)amidoanisole, which was freely soluble in the ordinary solvents except light petroleum, and had m. p. 75—76°. The base was identified by its *picrate* which crystallised from ethanol containing acetone in bright yellow needles, m. p. 118° (Found: C, 49·2; H, 5·0; N, 11·8. $C_{21}H_{28}O_5N_3S,C_6H_3O_7N_3$ requires C, 48·8; H, 4·8; N, 12·6%).

The above sulphonamide (45 g.) was mixed at 0° with sulphuric acid (300 g., 90%) and occasionally shaken until dissolved (14 hours). After 24 hours, the solution was added to ice and aqueous ammonia, the red syrupy precipitate being finally basified with sodium hydroxide. Ether extraction isolated the nitroamine as a deep red oil (29·5 g.) characterised by a *picrate*, crystallising from alcohol containing acetone in blood-red fine prisms, m. p. 113° (Found: C, 47·4; H, 5·3. $C_{14}H_{23}O_3N_3,C_6H_3O_7N_3$ requires C, 47·1; H, 5·1%).

6-*Methoxy*-9-γ-*diethylamino*-n-*propyl*iso*alloxazine Hydrochloride*, (II; R = OMe, *n* = 3).—The foregoing nitroamine (8·4 g.) was hydrogenated over palladised charcoal and condensed with alloxan in the presence of hydrochloric acid, as described for the preparation of (II; R = OMe, *n* = 2). The yield of dried product, m. p. 298—299° (decomp.), was 3·1 g., and a further 1·2 g. was precipitated on diluting the reaction solvent with ethanol. When alcohol was added to a solution of the salt in a little water, the hydrated hydrochloride (Found: Cl, 7·3%) slowly separated in clusters of orange needles, m. p. 300° (decomp.), from which was prepared the *picrate*, red tablets from ethanol–water, m. p. 261° (decomp. rapid heating) (Found after drying at 100°: C, 46·0; H, 4·4; N, 17·6. $C_{18}H_{23}O_3N_5,C_6H_3O_7N_3,2H_2O$ requires C, 46·3; H, 4·8; N, 18·0%).

2 : 4-*Dinitro-γ-diethylamino*-n-*propylaniline*.—The mixing of chloro-2 : 4-dinitrobenzene (2 g., 1 mol.) and γ-diethylamino-*n*-propylamine (1·3 g., 1 mol.) was accompanied by considerable evolution of heat, and the light brown resinous product crystallised on dissolving in alcohol. 2 : 4-*Dinitro-γ-diethylamino*-n-*propylaniline hydrochloride* separated in chrome-yellow prisms, m. p. 190—191° (Found : N, 16·5. $C_{13}H_{20}O_4N_4$,HCl requires N, 16·7%). The hydrochloride readily dissolved in water, and on addition of alkali the solid *amine* separated. Recrystallisation from a small volume of methanol gave deep yellow plates, m. p. 87—88°, which turned orange on long exposure to light (Found : C, 52·4; H, 6·7; N, 18·6. $C_{13}H_{20}O_4N_4$ requires C, 52·7; H, 6·7; N, 18·9%). When this was reduced in ethanol and combined with alloxan in presence of hydrochloric acid (3 mol.), a nearly black deliquescent amorphous solid was obtained which gave maroon-coloured solutions devoid of fluorescence, even in ultra-violet light.

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142. *The Preparation of 4-Aminophenyl Sulphones. Part I. The Reaction between Aromatic Sulphinic Acids and Quinones or Quinoneimines.*

By S. PICKHOLZ.

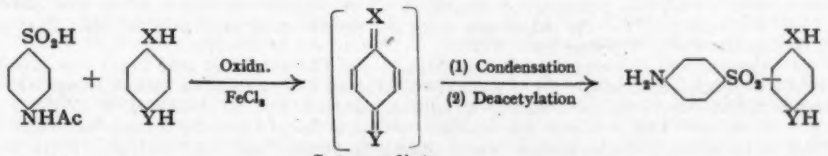
4-Aminophenyl sulphones have been prepared by the reaction between 4-acetamidobenzenesulphinic acid and quinones or quinoneimines or the corresponding dihydroxy- (or diamino-)benzenes. The compounds described possess high *in vitro* activity (against *B. subtilis*). Some of them are also active *in vivo* when tested on mice infected with *Str. Pyogenes* (var. *Aronson*).

THE interest attached in recent years to the high antibacterial activity of 4 : 4′-diaminodiphenyl sulphone has led to extensive work on rendering this compound less toxic for clinical use. The diacetyl, formaldehydesulphoxylate, and *NN′*-diglucosesulphonic acid derivatives are probably the best known examples. Only recently more attention has been directed to the preparation of other sulphones as possible chemotherapeutic agents. Starting from the assumption that the 4-aminophenylsulphonyl group is an essential part of any potential antibacterial sulphone, various investigators have described the preparation of unsymmetrical sulphones of the general formula $H_2N{\cdot}C_6H_4{\cdot}SO_2R$, where R is an aliphatic, aromatic, or heterocyclic group (Buttle *et al.*, *Biochem. J.*, 1938, **32**, 1101; Fourneau *et al.*, *Compt. rend. Soc. Biol.*, 1938, **127**, 393; Jensen and Lundquist, *Dansk Tid. Farm.*, 1940, **14**, 129; Roblin *et al.*, *J. Amer. Chem. Soc.*, 1941, **63**, 1930; Dewing *et al.*, *J.*, 1942, 239; Coggleshall and Maier, *J. Pharm. Exp. Ther.*, 1942, **76**, 161; Ochiai and Takubo, *J. Pharm. Soc. Japan*, 1941, **61**, 1; Bambas, *J. Amer. Chem. Soc.*, 1945, **67**, 668, 671; Burton and Hoggarth, *J.*, 1945, 14, 468; Goldberg and Besly, *ibid.*, p. 566; Walker, *ibid.*, p. 630).

The present paper represents a further contribution to the preparation of unsymmetrical 4-aminophenyl sulphones. The work was carried out in 1941 and 1942 * and is based in the main on the application of a method described first by Hinsberg in a number of papers (see Houben " Die Methoden der Organischen Chemie," 1930, 3e Aufl., Bd. III, 1281, 1329).

It consists in the oxidation–reduction of quinones or quinoneimines with aromatic sulphinic acids with the simultaneous formation of sulphones. The condensation will also take place by intermediate oxidation of the corresponding hydroxy- or amino-compounds in presence of the sulphinic acid. Potassium dichromate and ferric chloride are useful oxidising agents, and the method follows in principle the directions given by Hinsberg (*loc. cit.*; also Geigy A.-G., D.R.-P. 282,214). This feature considerably extends the scope of Hinsberg's reaction.

Starting with 4-acetamidobenzenesulphinic acid and deacetylating the condensation product, 4-aminophenyl sulphones are obtained which otherwise would be difficult to prepare. The reactions involved may be summarised as follows :



Intermediate quinone (quinoneimine)

In this way reactions were carried out with *p*-benzoquinone, *p*-toluquinone, quinol, *p*-aminophenol, *p*-phenylenediamine, and *p*-aminodimethyl- and *p*-aminodiethyl-aniline. Reaction with thymoquinone could not be effected (contrary to Hinsberg's claim, with benzenesulphinic acid). A few experiments with 4-chloro-, 4-nitro-, and 4-amino-benzenesulphinic acids have been included.

No attempts were made to determine the orientation of the sulphone group where unsymmetrical quinones or amines were used, and the constitutions ascribed to the compounds are therefore only tentative. For the *p*-toluquinone derivatives Walker's formulation (*loc. cit.*) is adopted. In the reactions with *p*-amino-dimethyl- and -diethyl-aniline it is assumed that the sulphone group owing to the directing influence of the amino groups

* Part of it was filed at the Patent Office on Feb. 6th, 1942, Serial No. 555,296 (August 16th, 1943). Publication delayed by an official secrecy order.

enters the *o*-position. This formulation is in accordance with the formation of *S*-(2-amino-5-dimethylaminophenyl)thiosulphuric acid (an intermediate in the preparation of methylene blue) by the oxidation of *p*-aminodimethylaniline with ferric chloride in presence of sodium thiosulphate (cf. Bernthsen, *Annalen*, 1889, **251**, 51). In *p*-aminophenol the sulphone group may be in the *o*-position to the hydroxyl group, which here would be expected to have the stronger directive influence. These formulations are in agreement with results to be described in a second paper, dealing with the reaction between sulphinic acids and aromatic nitroso compounds.

Except the sulphones from benzo- and tolu-quinone (Buttle *et al.*, *loc. cit.*; Burton and Hoggarth, *loc. cit.*; Walker, *loc. cit.*) none of the compounds has been described before. A German Patent (Schering A.G., D.R.-P. 740,515, 2nd Sept., 1943) claims the preparation of sulphones according to Hinsberg's method. So far only a short abstract with no experimental details (*Chem. Abs.*, 1945, **39**, 2296) has been available.

Tests *in vitro* for antibacterial activity (against *B. subtilis*) and *in vivo* for toxicity (on mice) support the claims put forward by Walker (*loc. cit.*) for the quinol derivatives. An attempt was made to condense the 4-amino-2′ : 5′-dihydroxydiphenyl sulphone with glucose. Though the solubility was increased, the antistreptococcal activity remained negligible. It is of particular interest that the 4-amino group apparently remained uncombined in this experiment.

The sulphones derived from the amines showed even higher antibacterial activities *in vitro* than the hydroxysulphones. Their activity *in vivo* [mice infected with *Str. pyogenes* (var. *Aronson*)] is remarkably increased, with 4 : 2′ : 5′-triaminodiphenyl sulphone approaching that of sulphanilamide, although they are generally more toxic.

Experimental.

4-Acetamidobenzenesulphinic acid was prepared from crude *p*-acetamidobenzenesulphonyl chloride (*Org. Synth.*, Coll. Vol. I, 7), and had m. p. 140—143° (decomp.). Material with higher m. p. as claimed in *Org. Synth.* was regularly found to be more or less decomposed. It is interesting to note that reductions carried out with pure sulphonyl chloride (recrystallised from chloroform) took much longer and gave much lower yields of the sulphinic acid. 4-Aminobenzenesulphinic acid was prepared by alkaline hydrolysis of the foregoing acetyl compound (Jensen and Lundquist, *loc. cit.*); owing to its low solubility in water and organic solvents it is less convenient to use. 4-Nitrobenzenesulphinic acid was prepared by the method of Zincke (*Annalen*, 1913, **400**, 1). 4-Chlorobenzenesulphinic acid was prepared from 4-chlorobenzenesulphonyl chloride by reduction with sodium sulphite; the acid melts at 106—108° (Gattermann, *Ber.*, 1899, **32**, 1142, gives m. p. 96—98°).

4-*Acetamido*-2′ : 5′-*dihydroxydiphenyl Sulphone*.—(*a*) 4-Acetamidobenzenesulphinic acid (20 g.) was dissolved in a mixture of hot water (100 c.c.) and ethanol (50 c.c.), and a hot solution of benzoquinone (10 g.) in ethanol (40 c.c.) added all at once with vigorous shaking. The deep brown mixture was almost instantly decolourised and the sulphone crystallised shortly afterwards. After ½ hour on the water-bath the product was filtered off and dissolved in dilute sodium hydroxide solution, and the red-brown solution filtered (charcoal). The solution was acidified with acetic acid; and the cream-coloured precipitate collected and dried (24 g.). A sample, recrystallised from 50% aqueous alcohol, had m. p. 271—272° (Found: S, 10·6. Calc. for $C_{14}H_{13}O_5NS$: S, 10·4%). (*b*) 4-Acetamidobenzenesulphinic acid (20 g.) and quinhydrone (20 g.) were caused to react as described under (*a*); the product was identical. (*c*) 4-Acetamidobenzenesulphinic acid (10 g.) was dissolved in a mixture of warm water (200 c.c.) and ethanol (20 c.c.), and a solution of quinol (4·5 g.) in warm water (100 c.c.) added. A solution of potassium dichromate (6 g.) in 4% sulphuric acid (120 c.c.) was slowly added to the mixture with continuous stirring at 50—60°. The dichromate was quickly reduced and a brownish precipitate formed. After complete addition, stirring was continued for 15 minutes, and the precipitate collected, washed with water, dried, and extracted with 90% ethanol (140 c.c.). The hot solution was filtered (charcoal), and the clear, slightly pinkish filtrate diluted with water (300 c.c.). After some hours the sulphone crystallised out. Recrystallisation from 50% aqueous alcohol gave 7 g., m. p. 270—272° [Buttle *et al.*, *Biochem. J.*, 1938, **32**, 1108, record m. p. 282° (corr.); Burton and Hoggarth, *loc. cit.*, 274°; Walker, *loc. cit.*, 273°].

4-*Amino*-2′ : 5′-*dihydroxydiphenyl Sulphone*.—(*a*) A mixture of the foregoing acetyl compound (25 g.), 32% hydrochloric acid (25 c.c.), 95% ethanol (40 c.c.), and water (70 c.c.) was refluxed for 2 hours, and the solution treated with charcoal, filtered, diluted with water (150 c.c.), and neutralised with sodium bicarbonate. The precipitate, recrystallised from hot water (charcoal), gave finally cream-coloured crystals (16—18 g.), m. p. 175—177° (Found: S, 12·2. Calc. for $C_{12}H_{11}O_4NS$: S, 12·1%). (*b*) A suspension of 4-aminobenzenesulphinic acid (8 g.) in hot water (80 c.c.) was shaken with a solution of benzoquinone (5 g.) in ethanol (50 c.c.). The sulphone was quickly formed, the colour being discharged. The solution was filtered hot with two additions of charcoal. The slightly pinkish solution was cooled; the sulphone then crystallised (11—12 g.), m. p. 178—180° after one more recrystallisation from 50% alcohol (Buttle *et al.* give m. p. 180°; Burton and Hoggarth, 180°; Walker, 176—177°).

4-*Acetamido*-2′ : 5′-*dihydroxy*-4′(?)-*methyldiphenyl Sulphone*.—(*a*) The sulphinic acid (6 g.) was dissolved in hot water (150 c.c.) and a solution of *p*-toluquinone (3·5 g.) in warm 50% ethanol (50 c.c.) added with stirring. Reaction took place immediately. The precipitate, recrystallised from 50% aqueous alcohol, had m. p. 236—238° (Walker gives m. p. 237—239°). Yield 8·5 g. (*b*) An identical product was obtained starting from 2 : 5-dihydroxytoluene and oxidising it with potassium dichromate in presence of the sulphinic acid (Found: S, 10·2. Calc. for $C_{15}H_{15}O_5NS$: S, 9·97%).

4-*Amino*-2′ : 5′-*dihydroxy*-4′(?)-*methyldiphenyl Sulphone*.—(*a*) Deacetylation was carried out as before in hydrochloric acid–ethanol–water. After recrystallisation from 50% aqueous alcohol 6·5 g. of aminosulphone were obtained from 10 g. of acetyl compound. (*b*) Condensation with 4-aminobenzenesulphinic acid and *p*-toluquinone gave the same product. Cream coloured crystals, m. p. 185—186° (Walker gives m. p. 187—188°) (Found: S, 11·3. Calc. for $C_{13}H_{13}O_4NS$: S, 11·5%).

4-*Acetamido*-2′ : 5′-*diacetoxydiphenyl Sulphone*.—4-Acetamido-2′ : 5′-dihydroxydiphenyl sulphone (9 g.) was boiled with acetic anhydride (15 c.c.) for 1 hour. The red solution was diluted with an equal amount of water and left overnight. The acetylated product crystallised out and was filtered off. It was dissolved in acetone (40 c.c.) and the solution filtered (charcoal). The filtrate was concentrated on the water-bath; the *sulphone* (8 g.) then separated. It had m. p. 181—182° (Found: N, 4·1; S, 8·3. $C_{18}H_{17}O_7NS$ requires N, 3·84; S, 8·2%). Hydrolysis with 2N-sodium hydroxide solution gave 4-amino-2′ : 5′-dihydroxydiphenyl sulphone.

4-*Acetamido*-2′ : 5′-*diethoxydiphenyl Sulphone*.—4-Acetamido-2′ : 5′-dihydroxydiphenyl sulphone (3·1 g.) was dissolved in 10% sodium hydroxide solution (10 c.c.) and ethyl sulphate (2·9 c.c.) added with shaking at 40—50°. The diethoxy compound suddenly precipitated; it was collected and recrystallised from 95% alcohol (50 c.c.) (charcoal). The *product*, pale, cream-coloured crystals, had m. p. 206—207° (2·5 g.) (Found: S, 9·05. $C_{18}H_{21}O_5NS$ requires: S, 8·8%).

4-*Amino*-2′ : 5′-*diethoxydiphenyl Sulphone*.—(*a*) By deacetylation in the usual way. White crystals, m. p. 204—205°;

(*b*) by ethylation of 4-amino-2′ : 5′-dihydroxydiphenyl sulphone in essentially the manner described above. The *products* were identical; mixed m. p. 204° (Found : S, 9·8. $C_{16}H_{19}O_4NS$ requires S, 10·0%).

5′-Amino-4-acetamido-2′-hydroxydiphenyl Sulphone.—(*a*) *p*-Aminophenol (5 g.) and 4-acetamidobenzenesulphinic acid (10 g.) were dissolved in warm water (150 c.c.), the solution was acidified with 50% sulphuric acid (40 c.c.), and 10% potassium dichromate solution (70 c.c.) was added with stirring (excess of dichromate should be avoided). The mixture was neutralised with sodium bicarbonate, and the brown precipitate collected, washed with water, and dried. The product was dissolved in ethanol (150—200 c.c.), and the dark solution repeatedly decolourised with charcoal until only slightly brown. The final filtrate was concentrated to *ca.* 50 c.c. and left for 24 hours in the cold. The crystals were collected and recrystallised from alcohol to yield white to cream-coloured needles (6—8 g.), m. p. 234—236°. (*b*) A solution of *p*-aminophenol (5 g.) and 4-acetamidobenzenesulphinic acid (10 g.) in warm water (200 c.c.) was acidified with concentrated hydrochloric acid (10 c.c.). A solution of anhydrous ferric chloride (16 g.) in water (160 c.c.) was added during 15 minutes with stirring, the temperature being kept at 50—60°. The stirring was continued for 1 hour, the dark coloured mixture cooled, and sodium bicarbonate added to give a pH of *ca.* 5·5—6; the dark precipitate was collected and worked up as before. The *substance*, crystallised from 80—85% aqueous acetone, had m. p. 235—236° (decomp.) (Found : S, 10·6. $C_{14}H_{14}O_4N_2S$ requires S, 10·5%).

4 : 5′-*Diamino-2′-hydroxydiphenyl Sulphone.*—Deacetylation of the foregoing compound (5 g.) with 10% hydrochloric acid (50 c.c.) and neutralisation of the filtered solution with sodium bicarbonate yielded the *sulphone*. Recrystallisation from ethanol or methanol gave white crystals (3 g.), m. p. 210—212° (decomp.) (Found : S, 12·1. $C_{12}H_{12}O_3N_2S$ requires S, 12·1%).

2 : 5′-*Diamino-4-acetamidodiphenyl Sulphone.*—Solutions of *p*-phenylenediamine (11 g.) dissolved in 5% hydrochloric acid (350 c.c.) and 4-acetamidobenzenesulphinic acid (22 g.) suspended in water (350 c.c.) with 10% sodium hydroxide (40 c.c.) were mixed and a solution of ferric chloride (35 g.) in water (140 c.c.) was added dropwise with vigorous stirring, the temperature being kept at 40—60°. The mixture was left for some hours, and the yellow solution then decanted from some tarry precipitate and filtered (charcoal). The filtrate was adjusted to pH *ca.* 5·5—6 with 10% sodium hydroxide (*ca.* 250 c.c.), and the brown precipitate collected, washed with water, dried, and twice recrystallised from 70% alcohol (100—150 c.c.). The *product* was dissolved in 10% hydrochloric acid (*ca.* 100 c.c.), the brownish solution decolourised with charcoal, and the filtrate neutralised with sodium bicarbonate. The white to cream crystals (12—16 g.) were collected, washed with water, and dried; m. p. 222—223° (Found : S, 10·6; N, 14·0. $C_{14}H_{16}O_2N_3S$ requires S, 10·5; N, 13·8%).

4 : 2′ : 5′-*Triaminodiphenyl Sulphone.*—The acetyl derivative (10 g.) was deacetylated in the usual way. The product was precipitated from the solution with ammonia and recrystallised twice from 25% alcohol. Almost white needles (6 g.) were obtained. The *sulphone* had m. p. 150—152° (Found : S, 12·0; N, 16·1. $C_{12}H_{13}O_2N_3S$ requires S, 12·2; N, 16·0%).

2′-*Amino-5′-dimethylamino-4-acetamidodiphenyl Sulphone.*—Dimethylaniline (16 g.) was converted into *p*-nitrosodimethylaniline, which was reduced with iron powder–hydrochloric acid to *p*-aminodimethylaniline. To the acid solution (corresponding to 14 g. of *p*-aminodimethylaniline), 4-acetamidobenzenesulphinic acid (22 g. in the equivalent amount of sodium hydroxide, total volume 220 c.c.) was added at once and the mixture stirred at 40—60°. 10% Ferric chloride (300 c.c.), acidified with concentrated hydrochloric acid (20 c.c.), was added in 15—20 minutes and the stirring continued for 1 hour more. After some time the greenish-white crystals of hydrochloride were filtered off. The product could be recrystallised from dilute alcohol or water; yield 15—16 g. This hydrochloride (8 g.) was dissolved in water (150 c.c.) with a few drops of concentrated hydrochloric acid, and the acid solution made neutral or slightly alkaline with ammonia or sodium hydroxide. The yellowish-green *acetyl* derivative was collected and washed with water, alcohol, and ether; 6·5 g., m. p. 217—219° (Found : S, 9·7; N, 12·8. $C_{16}H_{19}O_3N_3S$ requires S, 9·6; N, 12·6%).

4 : 2′-*Diamino-5′-dimethylaminodiphenyl Sulphone.*—The foregoing compound (3 g.) was deacetylated and the *sulphone* precipitated from the acid solution by excess of ammonia. The precipitate, recrystallised from ethanol, formed yellowish-green plates (2 g.), m. p. 190—192° (Found : S, 10·7; N, 14·5. $C_{14}H_{17}O_2N_3S$ requires S, 11·0; N, 14·4%).

2′-*Amino-5′-diethylamino-4-acetamidodiphenyl Sulphone.*—*p*-Aminodiethylaniline was prepared and condensed with 4-acetamidobenzenesulphinic acid under the same conditions as in the foregoing example (amine : acid : ferric chloride = 1 : 1 : 2). The *compound* (yield *ca.* 50%) formed yellow plates from benzene, m. p. 124—126° (Found : S, 9·1. $C_{18}H_{23}O_3N_3S$ requires S, 8·9%).

4 : 2′-*Diamino-5′-diethylaminodiphenyl Sulphone.*—Hydrolysis in the usual way yielded the *sulphone*, yellowish-green crystals from ethanol, m. p. 150—152° (Found : S, 10·2. $C_{16}H_{21}O_2N_3S$ requires S, 10·0%).

4-*Nitro-2′ : 5′-diaminodiphenyl Sulphone Hydrochloride.*—4-Nitrobenzenesulphinic acid (8 g.) and *p*-phenylenediamine (4·4 g.) were dissolved in hot water (160 c.c.) and the solution acidified with concentrated hydrochloric acid (30 c.c.); 20% ferric chloride solution (65—70 c.c.) was added at 70—80° with stirring during 15 minutes, the stirring continued without further heating for another 15 minutes, and the still warm solution filtered (charcoal). The yellow *product*, which crystallised out on cooling, was collected and recrystallised from 12—15% hydrochloric acid to give pale yellowish needles (6—8 g.), m. p. 257—260° (Found : Cl, 10·5; S, 9·9. $C_{12}H_{11}O_4N_3S,HCl$ requires Cl, 10·8; S, 9·8%). This compound was reduced with tin and hydrochloric acid to 4 : 2′ : 5′-triaminodiphenylsulphone, thus confirming the assumed structure.

4-*Chloro-2′ : 5′-diaminodiphenyl Sulphone.*—4-Chlorobenzenesulphinic acid (8 g.) and *p*-phenylenediamine (4 g.) were dissolved in 25% alcohol (100 c.c.) and the warm (50%) solution acidified with concentrated hydrochloric acid (20 c.c.). 20% Ferric chloride (40—50 c.c.) was added as before. The hydrochloride of the sulphone, m. p. 238—240°, crystallised out and was collected after some time. The *sulphone*, prepared by addition of a slight excess of dilute ammonia to a warm solution of the hydrochloride, crystallised from 90% ethanol in pale yellow crystals (7 g.), m. p. 146—148° (Found : S, 11·2. $C_{12}H_{11}O_2N_3ClS$ requires S, 11·3%).

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143. *Physical and Chemical Properties of Organo-metallic Compounds. Part II. The Oxidation of Zinc Alkyls.*

By C. H. Bamford and D. M. Newitt.

The kinetics of the oxidation of dimethyl-, diethyl-, and di-*n*-propyl-zinc have been studied. The technique used at low pressures consisted in the observation of pressure changes occurring when one reactant was admitted slowly to the other. It has been found that the methyl derivative oxidises more slowly than the higher alkyls. Oxidation ceases with the formation of $ZnMe_2O$, whereas with the higher alkyls ZnR_2O_2 may be formed. The reaction with the dimethyl is shown to be a chain process starting and ending on the walls. It is strongly catalysed by the solid reaction products. Possible mechanisms are discussed.

The kinetics of the oxidation of the zinc alkyls have been studied as part of a programme of work on spontaneously inflammable alkyls. The only previous measurements of this kind were made by Thompson and Kelland (J., 1933, 746) on dimethyl- and diethyl-zinc. These authors found that in the gas phase at low pressure a reaction of measurable rate occurs between the dimethyl and oxygen, leading to the formation of solid methylzinc methoxide, ZnMe·OMe. It was concluded that the reaction velocity is proportional to the pressure of the dimethyl and independent of the oxygen pressure. The addition of inert gas or a change in vessel diameter produced practically no change in rate. At higher pressures explosion was observed, the explosion limits being raised by a decrease in vessel diameter, by the addition of inert gas, or by a decrease in temperature. These results were considered to indicate a chain mechanism, which, however, was not discussed in detail by Thompson and Kelland.

The results of the present paper extend those of Thompson and Kelland to lower pressures, by the use of a different technique. In the main the earlier results are confirmed. It has been found, however, that the reaction rate is very markedly increased by the presence of solid reaction products. Further, at pressures near the ignition boundary, the rate is dependent upon the oxygen pressure, and is depressed by the addition of inert gas. It is shown later that the kinetic results are consistent with a chain mechanism in which chains start and end on the wall.

In a second paper Thompson and Kelland (J., 1933, 756) described their results with diethylzinc. They found that with this alkyl oxidation proceeds to the second stage ($ZnEt_2O_2$). The reaction was stated to be much slower than that of the dimethyl; in particular, ignition could not be obtained. The present results conflict with these observations and show that oxidation of $ZnEt_2$ can lead to $ZnEt_2O$ or $ZnEt_2O_2$ according to the conditions. Further, oxidation appears to be too fast to allow measurement, even down to the lowest pressures, and ignition occurs even more readily (*i.e.*, at lower pressures) than with $ZnMe_2$.

Dipropylzinc resembles the diethyl in undergoing an extremely rapid oxidation. Thus the oxidation of dimethylzinc differs from that of the higher alkyls in that under similar conditions it is a much slower process. A similar phenomenon occurs with the alkyls of the other elements studied (boron, antimony), and is discussed in Part III of this series.

All the alkyls investigated oxidise rapidly at pressures far below the lower ignition limits. In this respect these oxidations differ from many other chain reactions in which the transition between very slow reaction and ignition occurs abruptly over a comparatively small pressure range. The kinetic implications of this behaviour are discussed in Part III.

Experimental.

(A) *General Technique for Investigation of Reactions at Low Pressures.*—The method consists in the observation of the pressure changes which occur when one reactant is slowly admitted to the other in a thermostated reaction vessel. Usually oxygen was admitted to the vapour of the alkyl, at pressures of alkyl up to a few mm. The oxygen was stored in a large bulb at approximately atmospheric pressure. Its rate of admission was controlled by a capillary leading to an inlet tube which terminated near the centre of the reaction vessel. The latter was spherical, with diameter 8 cm., and was immersed in a thermostat which was usually kept at 25·0° ± 0·1°. The reaction vessel communicated with a manometer containing concentrated sulphuric acid through a capillary about 30 cm. long and of 0·5 mm. internal diameter. A travelling microscope with micrometer eyepiece allowed pressure changes of 0·01 mm. to be read with ease. In some cases a small amount of reaction between the acid and the alkyl vapour occurred, leading to initial instability of the manometer. This disappeared after short standing, as the small quantity of permanent gas produced exerted a strong buffering action in the capillary tube between the reaction vessel and manometer. The admission of oxygen was not started until the pressure had been steady for a few minutes. The alkyl was stored in a small trap at −80°. This was frequently evacuated to prevent accumulation of decomposition products. When it was decided to admit the vapour of the alkyl to oxygen in the reaction vessel, the liquid was first vaporised into a storage bulb.

The whole apparatus could be evacuated by a three-stage mercury diffusion pump and a Hyvac pump. In addition, a Toepler pump enabled gaseous products to be withdrawn for analysis.

Fig. 1 illustrates some features of the pressure–time (p–t) curves obtained. Actually, it is typical of the curves given by diethylzinc. The initial pressure of the alkyl is taken as the zero of pressure in the diagram. If no reaction occurred, the pressure–time curve would be the straight line OA, representing the entry of oxygen to the reaction vessel at a constant rate. Actually, reaction is accompanied by a reduction in volume, and on admission of oxygen the total pressure falls, as indicated by OB. The rate of contraction at any moment is given by the difference in the slopes of OA and the p–t curve. At the "reversal point" B, the rate of contraction just equals the rate of admission of oxygen, and the p–t curve is parallel to the time axis. After B is passed, the rate of contraction is less than the rate of admission of oxygen, and the pressure begins to increase. Eventually, when reaction is complete, the p–t curve becomes parallel to OA. The total contraction due to reaction of the initial pressure of the alkyl is then given by the final value of the vertical distance ab. If it can be assumed that the course of the reaction does not change as the experiment proceeds, this enables rates of contraction to be transformed into rates of reaction.

The p–t curve does not always start off with a negative slope. If the reaction is very slow, as in the case of dimethylzinc, the initial portion of the curve may be indistinguishable from OA (see, *e.g.*, Fig. 3). In such cases it is convenient, after admitting the oxygen for a known time, to cut off the gas, and follow the pressure changes.

The " sharpness " of the curve near the reversal point is an indication of the rate of reaction—a rapid reaction leading to a sharp reversal point, and *vice versa* (cf. Figs. 1 and 3).

In studying these reactions at low pressures it is often difficult to decide whether one is dealing with a partly or wholly homogeneous, or a completely surface process. Since a number of alkyls produce non-volatile solids on oxidation, this point could frequently be decided by using the Tyndall beam phenomenon. On focusing a cone of light from a carbon arc into the reaction vessel it was often possible to observe the formation of solid particles in the gas phase, and to distinguish the zone of precipitation fairly clearly. Detailed descriptions of the phenomena observed are given below.

(B) *Reactions at Higher Pressures.*—A spherical reaction vessel, 6 cm. in diameter, immersed in a water thermostat at 25° ± 0·1° was used in these experiments. Pressures were measured by a glass Bourdon gauge, reading to 0·03 mm. of mercury. After the desired pressure of the alkyl had been admitted, a known pressure of oxygen was added as quickly as possible, by momentarily opening a tap leading to a measuring vessel containing oxygen. The pressure of oxygen entering the reaction vessel was calculated from the decrease in pressure in the measuring vessel.

Generally, the reaction vessel was cleaned between runs by washing with dilute nitric acid and distilled water. This treatment was found to lead to reproducible results.

(C) *Preparation and Purification of Materials.*—(i) *Alkyls.* The preparation and purification of the alkyls have been described in Part I (this vol., p. 468). (ii) Oxygen was taken from a cylinder, passed over heated platinised asbestos, and condensed in a trap in liquid nitrogen. The liquid was then allowed to vaporise slowly, the first and the last third being rejected. (iii) Nitrogen was obtained from a cylinder, passed through a liquid-air trap, and used without further purification. (iv) Carbon dioxide was also obtained from a cylinder, frozen in liquid air, and fractionated in a vacuum.

(D) *Results.*

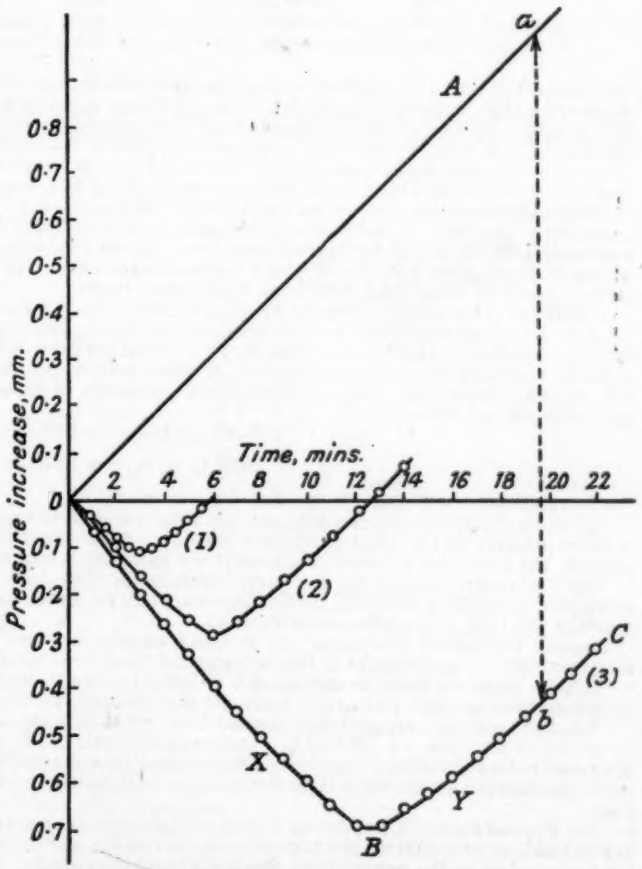
(1) *Diethylzinc.*—(a) *The reaction at low pressures.* A series of p–t curves obtained by admitting oxygen to diethylzinc vapour is shown in Fig. 1. In these experiments the reaction vessel was washed with dilute nitric acid and distilled water before each run.

The rate of entry of oxygen was in all cases 0·052 mm./min. In addition to these experiments, further runs were carried out with lower pressures of the alkyl, the lowest used being 0·02 mm. with a rate of admission of oxygen of 0·004 mm./min. In these runs an immediate contraction followed the addition of oxygen, the p–t curves being similar to those of Fig. 1. Thus, at pressures of diethylzinc greater than 0·02 mm. the reaction is too fast to be measured with this technique. Data obtained from the p–t curves are collected in Table I.

The p–t curve for run 4 is omitted from Fig. 1 for the sake of clarity; it follows that of run 3 very closely.

In runs 6 and 7 (Table I), the oxygen was stopped shortly after the reversal point had been passed, and the volatile products were then fractionated and analysed (Table II).

FIG. 1.



Admission of oxygen to diethylzinc. Initial pressures of $ZnEt_2$: (1) 0·21 *mm.*, (2) 0·45 *mm.*, (3) 0·95 *mm.*

TABLE I.

No. of run.	Initial p_{ZnEt_2} (mm.).	Initial slope, mm./min.	O_2 added at reversal point (mm.).	$\frac{O_2}{p_{ZnEt_2}}$.	Total contraction / p_{ZnEt_2}.
1	0·21	0·044	0·16	0·78	1·47
2	0·45	0·059	0·3	0·67	1·46
3	0·945	0·069	0·61	0·65	1·46
4	0·99	0·069	0·63	0·64	1·45
5	2·53	0·081	1·52	0·60	1·40
6	2·54	0·081	—	0·60	1·38
7	3·62	—	—	0·59	1·34

Four runs (8, 9, 10 and 11) in which the reactants were mixed in the reverse order (*i.e.*, alkyl admitted to oxygen) gave p–t curves of the same general shape as those of Fig. 1. Data from these experiments are given in Tables II and III.

Analysis of the volatile products in run 11 gave results similar to those obtained in 6 and 7 (see Table II).

An inspection of the p–t curves of Fig. 1 shows that the portions OB, BC, are not straight lines over their whole length: OB starts off in a rectilinear manner, but eventually at X begins to become slightly concave to the time axis. Similarly, BY is slightly concave, but the curvature rapidly diminishes and soon disappears. If the oxygen is cut off in

TABLE II.

No. of run.	Initial pressures, mm.	Products (mm.). Unsaturated hydrocarbon.	C_2H_6.	C_4H_{10}.	Total hydrocarbon / p_{ZnEt_2}.
6	2·54 } $ZnEt_2$	0·21	0·15	0·20	0·22
7	3·62 } $ZnEt_2$	0·30	0·27	0·33	0·25
11	2·01 O_2	0·15	0·20	0·13	0·24

TABLE III.

No. of run.	Initial p_{O_2} (mm.).	$ZnEt_2$ added at reversal point (mm.).	O_2 / p_{ZnEt_2}.	Total contraction / p_{ZnEt_2}
8	0·50	0·49	1·02	1·82
9	0·51	0·46	1·11	1·90
10	0·95	0·97	0·98	1·93

the ranges *OX* or *YO* no further contraction occurs, whereas in the ranges *XB*, *BY*, a slow contraction continues for a short time after stopping the oxygen. The curvature is thus due in part to the retardation in the diffusion of the gases in the range *XBY*, produced by the hydrocarbon formed during the reaction. In the main, however, the curvature of the *p*–*t* curve is probably due to a change in the course of the reaction as the pressure of diethylzinc decreases (see below). The point to be emphasised here is that only a very small amount of reaction occurs when the oxygen is stopped. This, together with the fact that rapid reaction occurs down to pressures of diethylzinc as low as 0·02 mm., shows that the reversal point must be close to the " end-point " of the reaction. The relative volumes of oxygen and alkyl reacting, as calculated from the reversal points, are given in col. 5 of Table I for runs 1—5, while col. 6 gives the ratio of the total contraction to the initial diethylzinc pressures. In the case of runs 6 and 7, the ratios are calculated from the analyses of the products after addition of excess oxygen to the alkyl. It will be seen that the figures for these runs fit into the general series of values obtained from the reversal times.

Table III gives similar ratios for the runs in which the reactants were mixed in the reverse order.

Course of reaction. Table I shows that for the higher pressures of diethylzinc, reaction is complete when the pressure of oxygen added is rather greater than half the initial pressure of the alkyl (see col. 5). On the other hand, when oxygen is present initially and the alkyl is added, it appears that approximately equal pressures of the compounds react (Table III, col. 4). Since only comparatively small quantities of gaseous products are formed, this suggests that the main reactions are as follows:

$$ZnEt_2 + \tfrac{1}{2}O_2 \longrightarrow ZnEt_2O(s) \text{ (excess } ZnEt_2) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

$$ZnEt_2 + O_2 \longrightarrow ZnEt_2O_2(s) \text{ (excess } O_2) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

In agreement with this are the following facts:

(i) From Table I it appears that, as the initial pressure of diethylzinc increases, the pressure of oxygen reacting with a given pressure of the alkyl diminishes steadily. This would be expected, since with a constant rate of admission of oxygen, the lower the pressure of the alkyl the more important reaction (2) becomes.

(ii) The initial slope of the *p*–*t* curve increases as the initial pressure of diethylzinc increases. This again may be attributed to an increase in the relative importance of (1) under these conditions, since for a given addition of oxygen, this reaction will lead to the greater contraction.

During the course of a single run in which oxygen is added to the alkyl, (1) will steadily decrease in importance relative to (2). This will lead to the curvature of the *p*–*t* curves observed experimentally (see also above).

It may be noted that Thompson and Kelland (*loc. cit.*) concluded that equal pressures of the reactants take part, with formation of solid $ZnEt_2O_2$. They did not identify reaction (1).

The hydrocarbons are probably formed from ethyl radicals, which result from collisions between the alkyl and hot molecules of products, *e.g.*, $ZnEt_2O_2$. In agreement with this it was found that the more rapidly the oxygen was added the greater the yield of hydrocarbons. Thus values for the ratio hydrocarbon/$ZnEt_2$ up to 1·3 may be obtained for fairly rapid additions. At the same time the solid product, instead of being white, acquires a darker colour and contains free zinc.

The Tyndall beam. On focusing a beam of light into the reaction vessel, it was found that the Tyndall beam becomes evident almost immediately the admission of the oxygen starts. For moderate diethylzinc pressures (*ca.* 1 mm.) there is a zone surrounding the oxygen inlet where the beam is invisible. This zone, in which there is little precipitation of solid, probably contains mainly oxygen, since the alkyl vapour has to diffuse against the oxygen stream. The oxygen may sweep out the solid particles mechanically, or alternatively the nuclei may not have sufficient time to grow to a size suitable for producing the beam during their stay in this region. Surrounding the central zone is a region of strong precipitation becoming feebler towards the wall of the vessel. As the initial pressure of diethylzinc increases, the central zone and the zone of precipitation contract, until at 10 mm. the precipitation region alone is visible as a line extending from the inlet tube. The Tyndall beam disappears sharply at the reversal point of the *p*–*t* curve, suggesting that the particles producing it rapidly coalesce and/or settle on the walls. These experiments provide strong evidence for the occurrence of a homogeneous gas reaction and suggest that the main reaction is homogeneous. At very low pressures of diethylzinc—*ca.* 0·05 mm.—no Tyndall beam could be obtained. This is probably due to the extremely low stationary concentration of particles formed in these circumstances. Thus there is no proof that the reaction is homogeneous at these low pressures, but there is no reason to believe it heterogeneous.

A number of experiments were carried out without the beam of light to ascertain whether any luminescence occurred during reaction. None could be observed. This applies also to dimethyl- and dipropyl-zinc.

(b) *The reaction at higher pressures.* When a sufficiently high pressure of oxygen is added to diethylzinc at pressures above about 4 mm. ignition occurs, accompanied by either a red or a blue flash, depending on the pressure of oxygen. Higher pressures give blue flashes. In some cases, with intermediate oxygen pressures, both kinds of flash were observed simultaneously, the blue being near the centre of the reaction vessel, and surrounded by the red. Fig. 2 shows the ignition limits. The " hatched " area in the diagram represents the region of pressure in which both types of flash are observed together. No spectroscopic observations of these flashes have been made. It is interesting to note, however, that the ignition emission spectrum of zinc contains two strong lines in the visible, situated at 6103 and 4912 A. respectively, which may be responsible for the red and the blue flashes.

A similar curve has been obtained by using dry air instead of oxygen. In this case only red flashes can be obtained.

Ignition is always accompanied by the formation of a black deposit containing metallic zinc on the reaction vessel.

These results are in disagreement with those of Thompson and Kelland. The cause of the discrepancy is not clear. Since Thompson and Kelland worked at about 50° and noted a considerable amount of attack by the alkyl on the tap grease used, it is possible that the diethylzinc vapour became contaminated in their experiments.

(2) *Dimethylzinc.*—(a) *The reaction at low pressures.* (i) Determination of Ratio of Reactants. Preliminary investigations showed that the reaction between dimethylzinc and oxygen is comparatively slow, with the result that there is no well-defined reversal point in the p–t curve. It is therefore necessary to determine the relative pressures reacting by another method.

Oxygen was admitted at a known rate to the reaction vessel containing the alkyl vapour at a known pressure. After about ½ hour's standing no further change in pressure occurred. The products were separated by low-temperature fractionation, and analysed. The results of a typical experiment are given below, all pressures being given in mm. :

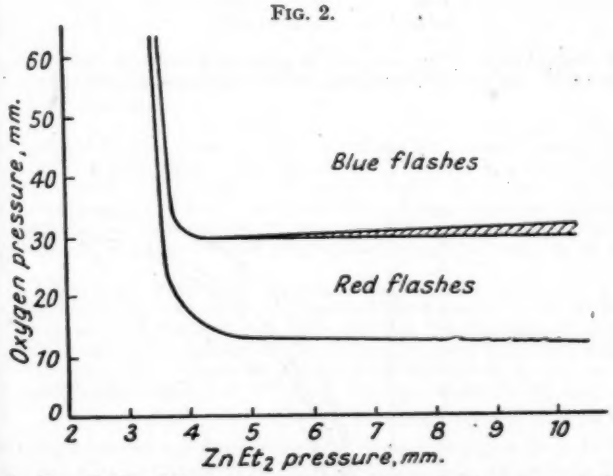
Initial pressure $ZnMe_2$	6·35	Final mixture consisted of			
O_2 added	1·37	CO	0·10	C_2H_6	0·08
Final pressure	4·20	CH_4	0·70	$ZnMe_2$	3·30

A white non-volatile solid was formed during reaction. From the above experiment it is seen that 3·05 mm. of the dimethyl react with 1·37 mm. of oxygen, giving a contraction of 3·52 mm. This agrees with the main reaction

$$ZnMe_2 + \tfrac{1}{2}O_2 \longrightarrow ZnMe{\cdot}OMe \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

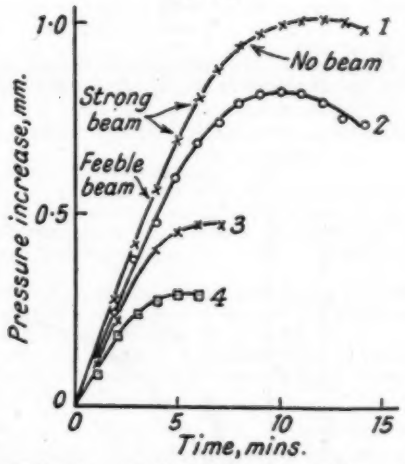
According to this, the ratios $O_2/ZnMe_2$ and contraction/$ZnMe_2$ should have values of 0·5 and 1·5 respectively, whereas in the above experiment the values are 0·45 and 1·15. The discrepancies are probably due to the formation of carbon

FIG. 2.



Ignition limits of diethylzinc. Spherical vessel, diam. 6 cm., 25°.

FIG. 3.



Oxidation of dimethylzinc: Effect of products on reaction rate. Initial pressure of O_2: 10 *mm. Rate of entry of* $ZnMe_2$: 0·154 *mm./min.*

monoxide and hydrocarbons. The latter correspond to the decomposition of 0·45 mm. of dimethylzinc, or about 14% of the total (reckoned on a carbon basis), leaving 2·62 mm. of alkyl to react with 1·37 mm. of oxygen, according to (3), if it is assumed that no oxygen enters into the reaction forming hydrocarbons.

A few runs were done at higher pressures, about 50 mm. of oxygen being rapidly added to approximately 6 mm. of dimethylzinc in the reaction vessel. Under these conditions it was found that practically no ethane was formed but the volume of methane increased, and corresponded to 15—17% of the alkyl oxidised. In these experiments, in which the initial mixture was close to the ignition limit, it seems that (3) still represents the main reaction.

A second series of experiments was done in which (excess of) oxygen was present initially in the reaction vessel. The following results (pressures in mm.) are typical of this series.

Initial pressure O_2	10·65	Final mixture consisted of			
$ZnMe_2$ added	10·75	O_2	4·86	CH_4	0·68
Final pressure	6·83	CO	0·32	C_2H_6	0·67

Thus 10·75 mm. of alkyl react with 5·79 mm. of oxygen to give the solid product together with the relatively small quantities of hydrocarbons and carbon monoxide. In this case also it is therefore clear that (3) represents the main reaction. The carbon monoxide and hydrocarbons correspond to 1·18 mm. of dimethylzinc, on a carbon basis, *i.e.*, about 11% of the total alkyl reacting.

These results show that even when excess of oxygen is employed, oxidation of dimethylzinc, unlike that of the diethyl compound, occurs only to the first stage, $ZnMe_2O$.

(ii) Pressure–Time Curves. The effect of surface. Although reaction is accompanied by contraction, an initial increase in pressure was always obtained on admitting dimethylzinc to oxygen (see Fig. 3). During the first few minutes reaction is extremely slow, but as the pressure of the alkyl builds up the rate increases, and the slope of the p–t curve becomes negative. These results are in marked contrast to those obtained with diethylzinc.

It was found that the solid product which accumulates during a run strongly catalyses the reaction. In this respect the latter resembles the oxidation of monogermane (Emeléus and Gardner, J., 1938, 1900). This effect is shown by Fig. 3. Curve 1 was obtained with the reaction vessel initially clean, while curves 2, 3, 4 refer to successive runs made without cleaning the vessel. A coating of paraffin wax on the inside of the vessel had no effect on the p–t curve.

The usual method of investigating the effect of surface, by packing the vessel with glass beads, was inapplicable in

this case, as it would interfere with the mixing of the gases. Attempts were made to obtain further information by using a smaller reaction vessel. Reproducible results could not be obtained with this, however. On examination it was found that the solid product was deposited in patches on the surface and not uniformly as with the larger vessel. The non-reproducibility was probably bound up with this.

The effect of foreign gases on the reaction rate. The addition of nitrogen was found to have little effect on the rate of reaction; the tendency was, however, to increase it slightly. The addition of the vapours of methyl or ethyl iodide was also without appreciable effect on the reaction rate.

The order of reaction. The strong catalytic effect of the solid products makes the determination of the order of reaction difficult and uncertain. The method used consisted in starting with a known pressure of oxygen in the reaction vessel, adding dimethylzinc for a known time, then stopping the alkyl and observing the pressure changes. In all cases the rate of reaction was extremely slow, and it is considered that the initial rate of contraction corresponds to that in a clean vessel. It was found that the rate of reaction in any one run remained almost constant for a period longer than would be expected. This was probably due to the increase in rate due to contamination of the walls approximately balancing the decrease due to consumption of the reactants. Results are given in Table IV.

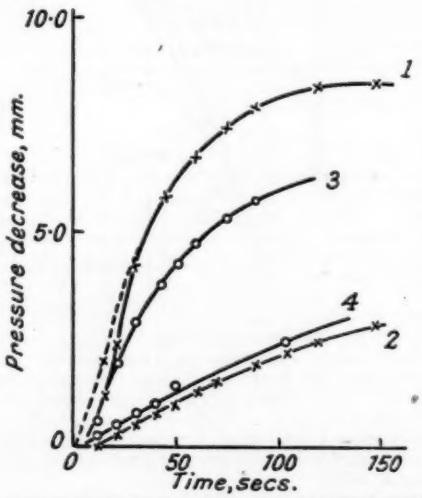
TABLE IV.

Initial pressure of O_2 = 1·62 mm.

Initial pressure, p, of $ZnMe_2$, mm.	Initial rate of contraction, w, mm./min. × 100.	100 w/p^2.	100 w (mm./min.) calc. from eqn. (8).
0·23	0·32	6·05	0·32
0·34	0·55	4·76	0·69
0·51	1·15	4·41	1·56
0·62	1·79	4·66	2·30
0·68	2·39	5·16	2·77

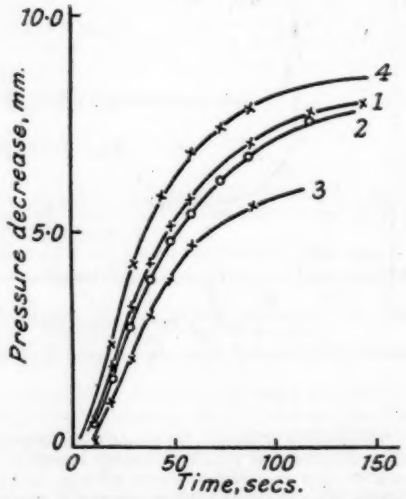
These results, with perhaps the exception of that at the lowest pressure, are very roughly in agreement with a bimolecular law, as shown in col. 3. As far as could be ascertained, the reaction is of zero order with respect to oxygen.

FIG. 4.



Reaction between dimethylzinc and oxygen: pressures in mm.
(1) $ZnMe_2$, 7·50; O_2, 30·8. (2) $ZnMe_2$, 3·85; O_2, 32·9.
(3) $ZnMe_2$, 7·50; O_2, 13·4. (4) $ZnMe_2$, 3·90; O_2, 15·3.

FIG. 5.



Effect of foreign gases on rate of oxidation of dimethylzinc: pressures in mm.
(1) $ZnMe_2$, 7·55; O_2, 34·5; N_2, 9·4. (2) $ZnMe_2$, 7·50; O_2, 31·0; N_2, 22·2. (3) $ZnMe_2$, 7·50; O_2, 31·8; CO_2, 30·5. (4) $ZnMe_2$, 7·50; O_2, 30·8.

In a " dirty " reaction vessel the reaction was of first order with respect to dimethylzinc, and of zero order with respect to oxygen. The velocity constant, obtained by plotting log [$ZnMe_2$] against time, has the value 0·034 min.$^{-1}$.

The Tyndall beam. Starting with oxygen in the reaction vessel, no beam could be obtained on admitting dimethylzinc unless the initial pressure of oxygen was above 3 mm. With higher pressures (10 mm.) the beam became visible after a few minutes and was fairly strong. It gradually faded, however, and finally disappeared (see Fig. 3). It is interesting that an increase in the pressure of oxygen enables a beam to be obtained, although it does not increase the rate of reaction.

Increasing the total pressure can assist precipitation by impeding diffusion to the walls. The disappearance of the beam may be explained if the condensation of vapour on the walls occurs much more readily when the latter have become coated with a solid film of product. Initially, with a comparatively high gas pressure, sufficient supersaturation is produced over a considerable volume of the vessel to cause precipitation of fine particles. These will then grow as the reaction preceeds, and will probably coalesce to some extent and settle on the walls. Any further deposition will then take place mainly on the walls, since the reaction is too slow to permit any appreciable supersaturation to be formed. In agreement with this, it was found that no beam can be obtained in a vessel in which a run has previously been carried out. The only alternative explanation is that in a dirty vessel the reaction is very largely heterogeneous. This is not acceptable, however; Fig. 3 shows that in a clean vessel a beam appears when about 0·5 mm. of dimethylzinc has been admitted. Now, in a dirty vessel pressures of this alkyl of 0·5 mm. may readily be reached. Thus, unless the presence of the solid on the walls of the reaction vessel suppresses the gas phase reaction (which seems very unlikely) this cannot be the true explanation.

(b) *The reaction at higher pressures.* The method used was similar to that described for the diethyl. Results are

shown in Figs. 4 and 5. Curves 1, 2, 3, and 4 of Fig. 4 are typical of runs carried out in a clean reaction vessel. At the higher pressures of dimethylzinc (curves 1 and 3) there is a short induction period, after which the reaction accelerates very markedly and then dies away. At the lower pressure of the alkyl (curves 2 and 4) there still appears to be an induction period, although the subsequent acceleration is less marked. A comparison of curves 1 and 3 shows that, when $p_{ZnMe_2} = 7{\cdot}5$ mm., the maximum rate is dependent upon the oxygen pressure, while curves 2 and 4 show that when $p_{ZnMe_2} \sim 3{\cdot}9$ mm., a considerable change in the pressure of oxygen has little effect on the rate (see also Table V). A series of runs with $p_{ZnMe_2} = 3{\cdot}9$ mm. and pressures of oxygen intermediate between those used in runs 2 and 4 confirmed this result.

TABLE V.

Run.	Pressure (mm.) of reactant at maximum rate. $ZnMe_2$.	O_2.	Maximum rate of contraction, mm./sec.	Calc. rate of contraction from eqn. (8), mm./sec.
1	6·20	30·3	0·37	0·37
2	3·85	32·9	0·024	0·023
3	6·76	13·1	0·13	0·11
4	3·90	15·3	0·024	0·019

Curve 5, the first portion of which is shown as a broken line in Fig. 4, was obtained with a dirty reaction vessel, using the same pressure as in run 1. The effect of the dirty surface is to remove the induction period completely, without producing any significant change in the maximum rate.

If the reaction follows the same course as in the low-pressure experiments, the total contraction with excess of oxygen present should be given by $[ZnMe_2]/0{\cdot}74$. The final contractions in the runs shown in Fig. 4 tended to approach this value.

The effect of foreign gases. Both nitrogen and carbon dioxide were found to reduce the rate of reaction to some extent, the latter being considerably more effective than the former. The curves are shown in Fig. 5.

Ignition. When suitable pressures of dimethylzinc and oxygen are mixed, ignition occurs, accompanied by a blue flash. In contrast to the results with the diethyl compound, no red flashes could be obtained. Near the ignition limit there is an induction period of a few seconds. The whole of the ignition curve was not determined. With $p_{ZnMe_2} = 8{\cdot}4$ mm., the limiting pressure of oxygen was found to be 45·0 mm. This is considerably higher than the limiting pressure for the same pressure of diethylzinc—*ca.* 12 mm.—in agreement with the slower oxidation of the methyl compound. This ignition limit was not changed when a dirty reaction vessel was used.

It may be noted that the pressures in run 1 (Fig. 4) are not very far removed from the ignition limits.

(3) *Oxidation of Mixtures of Dimethyl- and Diethyl-zinc.*—An investigation of the oxidation of these mixtures showed that the rate of reaction of the former with oxygen is not increased by addition of the latter alkyl. It may be concluded that active centres produced by the interaction of diethylzinc and oxygen react more readily with diethyl- than with dimethyl-zinc, *i.e.*, that chain propagation occurs less readily in the $ZnMe_2$–O_2 reaction and the average chain length is less.

(4) *Di-n-propylzinc.*—This reaction has not been studied in great detail. It was decided to ascertain (*a*) whether the reaction is slow (as with the dimethyl compound), or fast (as with the diethyl), and (*b*) whether it is predominantly homogeneous or heterogeneous. No detailed investigation of the nature of the products has been made.

Rate of reaction at low pressures. The *p*–*t* curves were very similar to curve *OBC*, Fig. 1, and show that the reaction is of the fast type. At the reversal point the pressure of oxygen added was approximately half the original pressure of the dialkyl, suggesting that the rapid reaction is similar to that occurring with diethylzinc, *i.e.*,

$$ZnPr_2 + \tfrac{1}{2}O_2 \longrightarrow ZnPr_2O \quad . \quad . \quad .

The fact that at low pressures the reaction is of zero order with respect to oxygen suggests very strongly that some surface process is involved. This is in agreement with the marked acceleration which occurs when the surface is coated with reaction products. Since there is undoubtedly a gas-phase reaction occurring, it seems likely that the oxidation is a chain process starting on the walls. In order to account for the observation that inert gases have no effect on the rate in the low-pressure experiments it must be further assumed that the chains also end on the walls. The observation by Thompson and Kelland (*loc. cit.*) that the rate of the " measurable " reaction is independent of vessel diameter is in agreement with this.

Turning to the runs at higher pressures, we may discuss the shape of the curves in Fig. 4. The initial lag and subsequent acceleration shown in Curves 1 and 3 may be accounted for in two ways. First, by analogy with the low-pressure experiments, the accumulation of solid product would be expected to lead to a gradual autocatalytic acceleration. Secondly, the curves are typical of branched-chain reactions, the rate increasing as the number of chains steadily builds up. Since the rate in these experiments increases with pressure of oxygen, the latter effect may be operative, with a branching reaction involving oxygen in a suitable manner. Curves 2 and 4, Fig. 4, show that with the pressures used in these experiments branching is less marked.

A general reaction scheme for the oxidation of dimethylzinc at low pressures is as follows, A and B being the chain carriers.

Initiation (wall) :	$ZnMe_2 + O_2 \longrightarrow A +$	(I)
Chain :	$A + ZnMe_2 \longrightarrow B +$	(II)
	$B + O_2 \longrightarrow ZnMe_2O_2 + A$	(III)
Chain ending (wall) :	$A \longrightarrow$	(IV)
	$B \longrightarrow$	(V)
Chain branching :	$B + ZnMe_2 + O_2 \longrightarrow A + B +$	(VI)

Since $ZnMe_2O_2$ is not the final product, a further reaction must be assumed :

$$ZnMe_2O_2 + ZnMe_2 \longrightarrow 2ZnMe_2O \quad . . . . . \quad (VII)$$

If it is assumed that (VII) is fast compared to the other reactions, then the rate of reaction given by the above scheme [neglecting the consumption of $ZnMe_2$ in (I) and (VI)] is

$$-\frac{d[ZnMe_2]}{dt} = k_1k_2[ZnMe_2],f\{[ZnMe_2],[O_2]\} \times \frac{2k_3[O_2] + k_5}{k_4k_5 + k_3k_4[O_2] + k_2k_5[ZnMe_2] - k_2k_6[ZnMe_2]^2[O_2]} \quad . . \quad (5)$$

where $k_1 f\{[ZnMe_2],[O_2]\}$ s the rate at which A centres enter the gas phase, from (I). It will be shown below that the experimental observations at low pressures with a dirty vessel are accounted for if $k_5 = 0$, and $f =$ constant. This latter assumption is reasonable, as many surface reactions are of zero order. In clean vessels, it must be assumed that $f = [ZnMe_2]$. These assumptions regarding f are equivalent to assuming that the film of products adsorbs the alkyl and oxygen strongly, and becomes saturated at low pressures.

Putting $k_5 = 0$ in (5), we obtain the equation

$$-\frac{d[ZnMe_2]}{dt} = 2k_1k_2[ZnMe_2]f\{[ZnMe_2],[O_2]\} \times \frac{1}{k_4 - k_2k_6[ZnMe_2]^2/k_3} \quad . . . . . \quad (6)$$

Both k_1 and k_4 will depend on the total gas pressure : they may be assumed to be inversely proportional to the total pressure (X). Further, when branching is important the rate will depend on the vessel diameter (d). This introduces a factor d^2 into the branching term in (6) (see, *e.g.*, Lewis and Van Elbe, " Combustion, Flames & Explosions of Gases," Camb. Univ. Press, 1938, Ch. I). Thus (6) becomes :—

$$-\frac{d[ZnMe_2]}{dt} = 2k_1'k_2[ZnMe_2]\,f\{[ZnMe_2],[O_2]\} \times \frac{1}{X\left(\frac{k_4'}{X} - \frac{k_2k_6}{k_3}[ZnMe_2]^2d^2\right)} \quad . . . . . \quad (7)$$

where k_1', k_4', and k_6' are constants.

At low pressures of reactants the branching reaction (VI) will be negligible. Under these conditions, if we make the above assumptions about f, (7) predicts rates which are independent of $[O_2]$ and the total pressure and are proportional to $[ZnMe_2]^2$ and $[ZnMe_2]$ in clean and in dirty vessels respectively. This is in agreement with observation.

In the high-pressure runs represented by curves 1 and 3 of Fig. 4, $X \sim \{[O_2] + [ZnMe_2]\}$ and (VI) is no longer negligible. The reaction velocity should thus increase with increase in $[O_2]$, as found experimentally. When inert gas, *e.g.*, nitrogen, is present, $X \sim \{[O_2] + [N_2] + [ZnMe_2]\}$. Thus the velocity should increase with increase in $[N_2]$. In practice, however, inert gas causes a small decrease in velocity. This indicates that the inert gas is suppressing the branching reaction. It may do this, for example, by partial deactivation of B, which while leaving (III) unaffected may suppress (VI).

Qualitatively therefore (7) is in satisfactory agreement with experiment. Equation (8), which is of the same form as (7) with $f = [ZnMe_2]$ and $X = \{[ZnMe_2] + [O_2]\}$, gives reaction rates which are reasonably close to the observed one in clean vessels over the whole pressure range (rate in mm./sec.; concentrations in mm.). The experimental and calculated values are compared in Tables IV and V.

$$\text{Rate of contraction} = -\frac{d[ZnMe_2]}{dt}/0{\cdot}74 = \frac{[ZnMe_2]^2}{1000 - 1{\cdot}78 \times 10^{-3}d^2\{[ZnMe_2] + [O_2]\}[ZnMe_2]^2} \quad . . . \quad (8)$$

According to (7) a chain isothermal explosion should ocur when

$$\frac{k_2k_6'}{k_3}[ZnMe_2]^2\{[ZnMe_2] + [O_2]\}d^3 = k_4' \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (9)$$

Thompson and Kelland (*loc. cit.*) reported that in a cylindrical vessel ($d = 4{\cdot}5$ cm.), $[ZnMe_2]^2[O_2]$ was constant at the ignition boundary. This was not so in a narrower vessel ($d = 2{\cdot}5$ cm.). In this case $[ZnMe_2]^2\{[ZnMe_2] + [O_2]\}$ is more nearly constant than the simpler expressions, although not satisfactorily so.

Presumably the ignition region is bounded by a closed curve, which is determined by reaction (IV), and chain-breaking reactions at higher pressures not shown in the above scheme. Thompson and Kelland located a portion of this boundary, but the lay-out of the remainder is unknown, and would probably be difficult to determine for practical reasons. In the absence of this information, and without knowledge of the variation of reaction rate over wider ranges of pressure of reactants than is now available, it is not fruitful to discuss the conditions for ignition much further. It may be noted, however, that (8) and (9) predict explosion at pressures rather lower than found experimentally. Thus with $[O_2] = 45$ mm. ($d = 6$ cm.), the calculated limiting pressure of $ZnMe_2$ is 5·5 mm., whereas the experimental value is 8·4 mm. This may imply that some chain breaking by oxygen is going on even at these pressures. However, even in this region of pressures, the practical difficulties are considerable. During the lag before explosion a reaction occurs, so that the initial pressures are appreciably higher than those at the moment of explosion. Further, near the boundary, the time of addition of oxygen is sufficiently large to cause uncertainty. If it is assumed that chain breaking by oxygen is not important at 45 mm. pressure, the above considerations seem to indicate that ignition is ultimately an isothermal chain process. This is in agreement with Thompson and Kelland's observation that the oxidation process has a very small temperature coefficient.

There are a number of possible alternatives for the chain carriers, *e.g.*, (i) A = O, B = $ZnMe_2O$, the latter being an excited molecule or radical. This scheme is possible energetically (unpublished values for the heat of combustion of $ZnMe_2$ obtained by Dr. L. H. Long). (ii) A = $ZnMe_2O_2$*, B = $ZnMe_2$*, giving a thermal chain. This mechanism would need the assumption that, while collisions between inert gas molecules and the active centres do not prevent the latter participating in (II) and (III), they deactivate B sufficiently to impede (VI).

Similar reactions may occur during the oxidation of diethyl- and dipropyl-zinc, except that the chain-propagating processes are much faster, relative to (VII). When diethylzinc is added slowly to excess of oxygen, the chain reaction is so rapid that $[ZnEt_2]$ is kept extremely low, and (VII) cannot occur to an appreciable extent. Thus the main product is $ZnEt_2O_2$. On the other hand, when oxygen is added to diethylzinc, (VII) is important, and $ZnEt_2O$ is formed. In other words, with dimethylzinc, (VII) is rapid compared to the chain-propagating reaction, while with diethylzinc all three reactions are about equally fast.

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144. *Physical and Chemical Properties of Organo-metallic Compounds. Part III. The Oxidation of Boron and Antimony Alkyls.*

By C. H. BAMFORD and D. M. NEWITT.

The kinetics of the oxidation of trimethyl- and tri-*n*-propyl-boron have been studied, using the technique described in Part II. The rate is slow enough to be measured only in the case of the trimethyl. This reaction is strongly inhibited by mixtures of boron trifluoride and water. The results are consistent with a chain process, beginning and ending in the walls. Possible reaction schemes are discussed.

The relative rates of oxidation of trimethyl- and triethyl-stibine have been investigated.

The oxidation of the boron and antimony alkyls, like that of the zinc alkyls described in Part II, exhibits the following features: (*a*) a rapid reaction occurs at pressures well below the ignition limit, and (*b*) reactions of the methyl derivatives are much slower than those of the higher alkyls. The significance of these points is discussed.

No systematic kinetic studies of the oxidation of the boron alkyls have hitherto been made, although a number of observations on the nature of the oxidation products are on record. Frankland (*J.*, 1862, **15**, 363) stated that slow oxidation of triethylboron produces the diethyl ester of ethaneboronic acid. Krause and Polack (*Ber.*, 1928, **61**, 278) and Krause and Nobbe (*Ber.*, 1930, **63**, 934) studied a number of alkyls, and concluded that the oxidation products were esters of aliphatic boronic acids, or alkylboron oxides. More recently, Johnson and van Campen (*J. Amer. Chem. Soc.*, 1938, **60**, 121) showed that tri-*n*-butylboron is oxidised by dry air to the dialkyl boronate, $BBu(OBu)_2$, exclusively, but with moist air the reaction stops at the half-way stage, BBu_2OBu. They concluded that the " anhydrous autoxidation is a stepwise process, in which the dialkylboronic ester is an intermediate, and that water inhibits further oxidation of the latter." Results described in the present paper are in agreement with the view that the slow oxidation of trimethylboron produces the ester $BMe(OMe)_2$. The reaction is shown to be a chain process, in which chains start and end in the walls, and are mainly without branching except near the ignition limits. As with the zinc alkyls, it appears that the methyl derivative oxidises much less readily than the higher alkyl.

This remark is also true for the antimony alkyls, which have only been studied briefly.

Experimental.

The experimental technique was essentially similar to that described in Part II. As with the zinc alkyls, two series of experiments were carried out: (*a*) the pressure–time curves were determined for slow admission of one reactant to the other contained in a reaction vessel in a thermostat, and (*b*) reaction rates at rather higher pressures were measured, the reactants being mixed as rapidly as possible.

Preparation of Materials.—The preparation and purification of the alkyls have been described in Part I. Boron trifluoride was prepared by heating a mixture of potassium fluoroborate and boric oxide (Hellriegel, *Ber.*, 1937, **70**, 689), and condensing the trifluoride in liquid air; after fractionation in a vacuum it was stored in a tube in liquid air. Oxygen and nitrogen were purified as described in Part II.

Results.

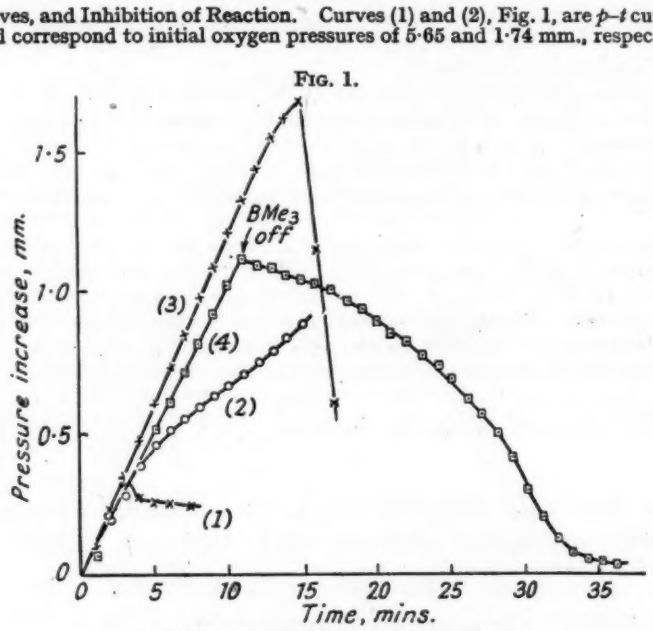
(1) *Trimethylboron.*—(a) *Reaction at low pressures.* (i) Determination of Ratio of Reactants. It was found that when the alkyl and oxygen were mixed at pressures which give rise to a slow reaction, the final total pressure was equal to the initial pressure of the reactant present in excess. This is true for all pressures in the range investigated (0·2—10 mm.). The products of reaction appear to be completely gaseous. It follows, therefore, that under the conditions of these experiments, 1 vol. of trimethylboron reacts with 1 vol. of oxygen to give 1 vol. of products.

The products are completely condensable in liquid air. When condensed into a small tube they form a colourless, rather viscous liquid with a characteristic smell. It is fairly stable to air and water and appears to be a single compound. The pressure relations show that it has the formula BMe_3O_2, or probably $BMe(OMe)_2$:

$$BMe_3 + O_2 \longrightarrow BMe_3O_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

(ii) Pressure–Time Curves, and Inhibition of Reaction. Curves (1) and (2), Fig. 1, are p–t curves for the slow admission of the alkyl to oxygen, and correspond to initial oxygen pressures of 5·65 and 1·74 mm., respectively. Little measurable

Fig. 1.



Admission of trimethylboron to oxygen.

Initial pressures:

(1) 5·65 *mm.* O_2.
(2) 1·74 *mm.* O_2.
(3) 5·12 *mm.* O_2 + 0·47 *mm.* BF_3.
(4) 5·97 *mm.* O_2 + 0·43 *mm.* BF_3.

Rate of entry of BMe_3: 0·131 *mm./min.*

reaction occurs during the first 2½ mins., but, with the higher pressure of oxygen, a rapid reaction starts at about 3 mins., and the p–t curve soon becomes horizontal. Under these conditions the rate of contraction is the same as the rate of entry of trimethylboron to the reaction vessel. The fact that runs have been made which give a horizontal portion of the curve extending over a considerable period agrees with equation (1). With the lower pressure of oxygen, the rate is never sufficiently high to give a horizontal portion. It will be noticed that after about 13 mins. the slope of the curve begins to increase, indicating the deceleration of the reaction owing to consumption of the oxygen.

One sample of trimethylboron gave abnormal results. This produced long induction periods (*ca.* 10 mins.) terminated by a very rapid contraction. It seemed likely that this was due to some impurity in the alkyl. Since the latter had been prepared by the Grignard method, possible impurities were ether, methyl iodide, and boron trifluoride. It was found that none of these substances alone has any appreciable effect on the reaction. However, boron trifluoride together with a trace of water is a powerful inhibitor; for instance, pretreatment of the reaction vessel by admission of 10 mm. of water vapour and evacuation for 4 mins. introduced sufficient water to give strong inhibition with the trifluoride. Curves (3) and (4), Fig. 1, give results for runs in a pretreated vessel, in the presence of boron trifluoride. The technique in these runs consisted in pretreating the vessel as described above, and adding the fluoride and then the oxygen. Since a slow contraction occurred when the fluoride was admitted to the pretreated vessel (owing presumably to reaction between boron trifluoride and water) the pressures of trifluoride given in Fig. 1 are only approximate. After the mixture had stood for some time to ensure homogeneity, the trimethylboron was admitted. Curve 3 shows that little reaction occurred during the first 12 mins., but just after 15 mins. a very rapid reaction took place. In run (4) the admission of the alkyl was stopped after 11 mins. A slow reaction followed which gradually accelerated, and became quite rapid

at 29 mins. These results show that the inhibitor is gradually destroyed during a run, its removal being accompanied by acceleration of the reaction.

The above procedure is unsatisfactory for quantitative investigation, since the pressures of boron trifluoride and water cannot be measured accurately. The preparation of a mixture of known composition was therefore tried by the following method. Mixtures of water vapour and oxygen, and boron trifluoride and oxygen, were made in separate vessels and allowed to stand until homogeneous. Measured pressures of these were mixed in the reaction vessel together with oxygen, to obtain a mixture of the desired composition. The following mixtures were made up in the reaction vessel in this way :

Mixture.	A.	B.	C.	D.
H_2O (mm.)	0·02	0·14	0·31	0·17
BF_3 (mm.)	0·42	0·43	0·43	0·80
O_2 (mm.)	5·99	5·91	6·10	5·10

None of the mixtures gave any inhibition. The experiment with D was repeated, with the difference that an interval of 20 mins. was allowed to elapse between introducing the water–oxygen mixture into the vessel and adding the trifluoride–oxygen, and then a further period of 20 mins. before adding the necessary oxygen. In this case there was marked inhibition, reaction starting 9 mins. after the admission of trimethylboron was started. The inhibitor thus appears to be produced comparatively slowly by interaction between the trifluoride and water under these conditions. This is not so, however, when boron trifluoride is added to the pretreated reaction vessel, as in the earlier runs, and it is probable, therefore, that the inhibitor-producing reaction is a surface process.

Nothing is known about the chemical nature of the inhibitor except that it results from reaction between boron trifluoride and water: it might be HF, HBF_4, or a compound produced by the attack of HF on the reaction vessel. The following experiments show that the inhibitor is volatile. A run was carried out in which boron trifluoride was added to the pretreated reaction vessel; the latter was then evacuated for 4 mins. Oxygen was then let into the vessel, and trimethylboron was admitted as usual. There was no inhibition. In a further experiment, a bulb of about the same size as the reaction vessel was pretreated with water vapour, after which the trifluoride and oxygen were added. A reaction carried out with this mixture would have been subject to strong inhibition. The mixture was transferred to the dry reaction vessel, and trimethylboron admitted immediately. An induction period of 29 mins. was observed, showing that the inhibitor had been transferred with the gas mixture to the reaction vessel.

The last experiment lends some support to the view that the inhibition is a homogeneous process. If this were not so, it would have to be assumed that the inhibitor, initially formed by a surface process, in the mixing vessel, becomes desorbed and then readsorbed on the surface of the reaction vessel. The latter process, however, would be slow, since a large excess of oxygen was present. It will be seen later that experiments at higher pressures also point to homogeneous inhibition.

All the runs described so far, with the exception of the last, were repeated in a reaction vessel coated with paraffin wax. This produced no significant difference in the results.

If it is assumed that in Run 3 (Fig. 1) each molecule of BF_3 produces one of inhibitor, a value of 50 is obtained for the chain length. This is a minimum value.

(iii) The Order of Reaction, and the Effect of Inert Gases. The results given in Table I were obtained by admitting trimethylboron at a rate of about 0·1 mm./min. to the reaction vessel containing a known pressure of oxygen. When the desired pressure of alkyl had been reached, the admission was stopped, and pressure readings were taken at suitable intervals. Allowance was made for the amounts of reactants consumed during the admission of the alkyl by comparing the actual pressure change during admission with that calculated from the rate of entry of the alkyl.

TABLE I.

Reaction Rates in Waxed Reaction Vessels : Temperature 24·8°.

Run.	Initial pressures, mm. × 10. BMe_3.	O_2.	Initial rate of contraction, w, mm./min. × 100.	$100\,w/[BMe_3][O_2]^2$.
1	1·38	29·0	2·80	2·41
2	0·97	29·7	1·84	2·15
3	1·46	15·35	0·735	2·14
4	2·70	15·36	1·52	2·39
5	2·89	7·76	0·38	2·18

TABLE II.

Reaction Rates in Unwaxed Vessel : Temperature 24·8°.

Run.	Initial pressures, mm. × 10. BMe_3.	O_2.	Initial rate of contraction, w, mm./min. × 100.	$100\,w/[BMe_3][O_2]^2$.	$100\,w/[BMe_3][O_2]$.
6	1·41	6·06	0·20	3·88	2·34
7	1·84	8·51	0·37	2·77	2·36
8	1·65	13·91	0·92	2·88	4·00
9	0·92	19·85	1·29	3·55	7·10
10	1·22	27·20	2·76	3·06	8·31
11	0·92	28·15	2·66	3·65	10·20
12	0·95	46·6	3·6	1·69	—
13	0·97	68·0	4·6	1·03	—
14	1·30	126·0	2·3	0·11	—

Table I shows that, in the range of pressures investigated, the rate is proportional to $[BMe_3][O_2]^2$. It is convenient to consider the runs in Table II in two groups; runs 6—11, which cover approximately the same pressure range as those of Table I, and 12—14 with considerably higher pressures of oxygen. With regard to the former group, the results, although not so satisfactory as those with the waxed vessel, seem to indicate that the rate follows a similar law, *i.e.*,

$$w = k[BMe_3][O_2]^2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

The values for the proportionality " constant " obtained by assuming dependence on the first power of $[O_2]$ are recorded in col. 6. They show a very marked trend which is absent from the figures in col. 5. Runs 12, 13, 14 show that at higher

pressures of oxygen the rate increases much less rapidly than $[O_2]^2$: in fact increasing $[O_2]$ beyond a certain value causes a decrease in w (runs 13, 14). This is almost certainly a diffusion effect; it is readily understandable if the reaction starts on the walls. Under these conditions the rate of diffusion of trimethylboron to the walls may be less than the rate of the surface reaction, with the result that a region of lower alkyl concentration exists near the walls, and gives rise to a rate which is lower than would be expected. In agreement with this view is the fact that addition of a comparatively large pressure of nitrogen cuts down the rate markedly. Thus a mixture containing BMe_3 0·1, O_2 2·91, N_2 9·61 mm. gave $\dot{w} = 1{\cdot}24 \times 10^{-2}$ mm./min., whereas in the absence of nitrogen the rate is approximately $2{\cdot}7 \times 10^{-2}$ mm./min. (run 11). A further effect noticed was that when comparatively high pressures of oxygen are used, the rate falls off more rapidly than would be expected during the course of a single run. This is also a diffusion effect.

The addition of moderate pressures of nitrogen has no measurable effect on the rate of reaction, as is evident from Table III.

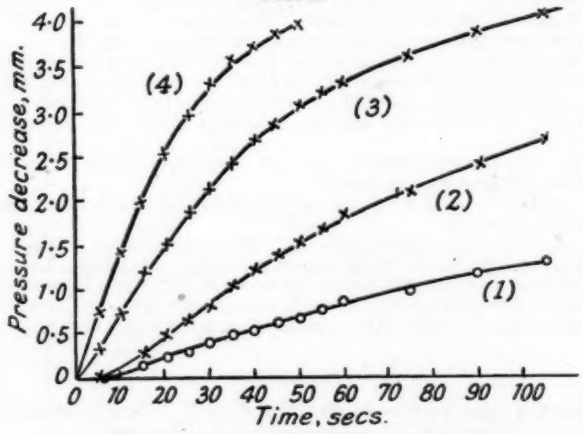
TABLE III

Temperature 24·8°.

Run.	Initial pressures, mm. × 10. BMe_3.	O_2.	N_2.	Initial rate of contraction, w, mm./min. × 100.
8	1·65	13·91	0	0·92
15	1·65	13·91	13·29	0·92
16	1·70	13·95	6·21	0·88

The absence of an inert-gas effect may be explained in a number of ways: (*a*) the reaction may be homogeneous, of the non-chain type, (*b*) it may be completely heterogeneous, (*c*) it may be a chain reaction in which chains begin and end on the walls, or (*d*) it may be a chain reaction in which chains begin and end, by a suitable mechanism, in the gas phase. The order of reaction, and the fact that ignition can be suppressed by an inhibitor eliminates (*b*), and the inhibition by

FIG. 2.



Reaction between trimethylboron and oxygen.

Initial pressures, mm.

	BMe_3.	O_2.		BMe_3.	O_2.
(1)	5·10	2·72	(3)	5·15	7·77
(2)	5·05	5·05	(4)	5·10	11·60

boron trifluoride–water mixture excludes (*a*). The effect of high pressures of oxygen or nitrogen in reducing the rate by impeding diffusion would appear to exclude (*d*), leaving (*c*) as the most probable alternative.

During the experiments described above, it was found that after the first few runs, reaction rates were satisfactorily reproducible. This is to be contrasted with the case of dimethylzinc, in which the solid oxidation products exert a strong catalytic effect.

(b) *The reaction at higher pressures.* (i) The Slow Reaction. The technique employed was similar to that described in Part II. The relations observed between total contraction and initial composition were the same as those described in section (a) (i) above, showing that the stoicheiometric reaction follows equation (1).

The pressure–time curves obtained are shown in Fig. 2, and the values of the maximum rate of contraction, w, are given in Table IV. The pressures of reactants given in the table correspond to the moment at which the rate is a maximum.

TABLE IV.

Temperature 25·0°.

Run.	Pressures, mm. BMe_3.	O_2.	w, mm./min.	$100\,w/[BMe_3][O_2]^2$.	$10\,w/[BMe_3][O_2]$.
1	4·6	2·2	0·94	4·2	0·93
2	4·1	4·1	2·4	3·5	1·43
3	3·9	6·5	5·2	3·2	2·05
4	4·3	10·8	11·1	2·2	2·40

From the figures in cols. 5 and 6 it would seem that the order of reaction with respect to oxygen is between 1 and 2—actually it is about 1·6. The value is only approximate, however, since the reacting mixture under the conditions of the experiment would almost certainly be inhomogeneous, especially at the higher pressures. Further, a rapid reaction would tend to maintain the inhomogeneity. Thus, the effect of the latter would probably be to retard the faster reaction

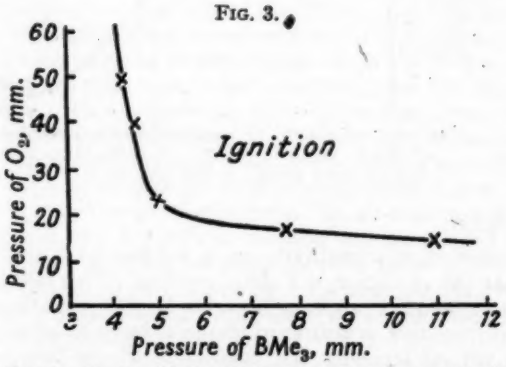
to a greater extent than the slower ones, *i.e.*, to lower the apparent order of reaction. It therefore seems reasonable to suppose that the true order with respect to oxygen is 2, as at lower pressures. The values for the ratio $w/[BMe_3][O_2]^2$ shown in Table IV, *viz.*, 2·2—4·2 × 10^{-4}, are in fact fairly close to the value obtained at lower pressures—*ca.* 3 × 10^{-4} (Table II). A smaller reaction vessel was used in the present experiments, but if, as suggested earlier, chains begin and end on the walls, this would not affect the rate of reaction appreciably. The pressures given in Table IV are not very near to the ignition limit, so that branching would probably be small.

(ii) Ignition. A portion of the ignition boundary is shown in Fig. 3. There were no appreciable induction periods. It was noticed that with the higher pressures of trimethylboron, and pressures of oxygen only slightly above the limit, a rather feeble bluish flash was produced. Lower pressures of the alkyl, however, gave a very intense green flash. By plotting the minimum total pressures required for ignition against the corresponding values for the mol.-fraction of trimethylboron, it is seen that ignition occurs most readily with the mol.-fraction equal to 0·35.

(iii) Inhibition. It was found that if the reaction vessel was pretreated with water vapour as described earlier, addition of boron trifluoride raised the ignition limit slightly, *i.e.*, made the mixture less reactive. The amount of water introduced in this way was insufficient to cause marked retardation of the slow reaction. The following pressures of vapours were introduced into the reaction vessel, and the oxygen added rapidly: H_2O, 0·74; BF_3, 2·0; BMe_3, 7·7; O_2, 9·9 mm. An extremely slow reaction ensued, the rate of contraction being about 0·25 mm./min., whereas in the absence of inhibitor the rate would have been approximately 22 mm./min.

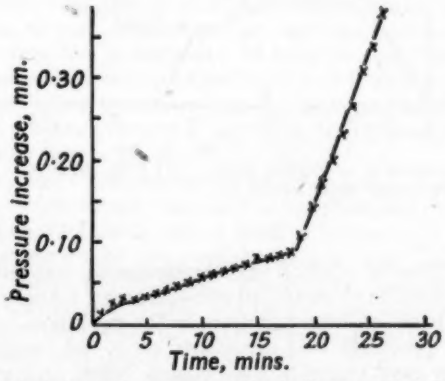
In another run the following pressures were used: H_2O, 0·74; BF_3, 0·9; BMe_3, 7·91; O_2, 47·0 mm. In this case also there was a very slow reaction. The pressures of alkyl and oxygen correspond to a point well inside the ignition region in the absence of inhibitor (see Fig. 3). Hence, both the slow and the explosive reaction are subject to inhibition.

FIG. 3.



Ignition limits of trimethylboron and oxygen; spherical vessel, diameter 6 cm., 25°.

FIG. 4.



Admission of oxygen to tripropylboron. Initial pressure: 1·16 mm. BPr_3. Rate of entry of O_2: 0·057 mm./min.

(2) *Tri-n-propylboron.*—The oxidation of this alkyl has only been briefly investigated. A typical pressure–time curve obtained at low pressure is shown in Fig. 4. The initial portion is almost horizontal; after a sharp "reversal" point the curve ascends steeply and almost linearly.

When the oxygen was stopped before the reversal point was reached no contraction occurred; further, the reaction mixture at this stage was rapidly and completely condensable in liquid air, showing that no appreciable pressure of oxygen was present. The pressures of oxygen added at the reversal point are very nearly equal to the initial pressure of the alkyl, as shown below:

Run	1	2	3	4
Initial press. of BPr_3, mm.	1·49	0·55	0·29	1·16
Pressure of O_2 added at reversal point, mm.	1·43	0·53	0·29	1·03

These facts suggest that the initial portion of the *p*–*t* curve corresponds to an oxidation following the equation

$$BPr_3 + O_2 \longrightarrow BPr_3O_2(g) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

proceeding at a rate which is always too fast to be measurable with the present technique. The small expansion before the reversal point may indicate the occurrence to a small extent of another reaction accompanied by an increase in volume.

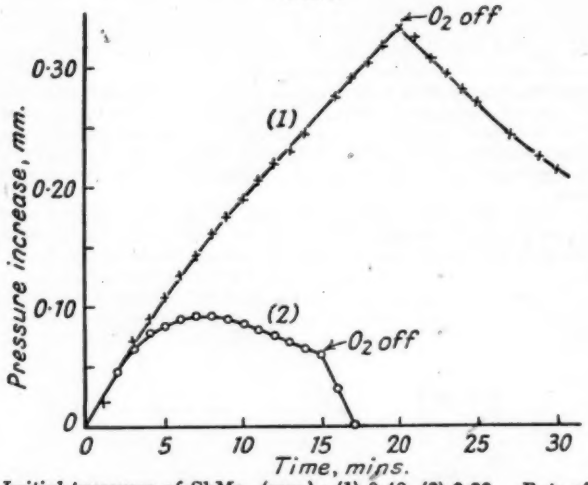
The rate of increase of pressure after the reversal point was always considerably less than the rate of entry of oxygen (see Fig. 4). This may be due to a further slow oxidation of BPr_3O_2 to *n*-propyl borate.

Preliminary experiments with boron trifluoride–water mixtures indicated the existence of short induction periods showing that the oxidation of tripropyl- like that of trimethyl-boron is subject to inhibition.

(3) *Antimony Alkyls.*—The pressure–time curves obtained by the admission of oxygen to the vapours of trimethyl- and triethyl-stibine are shown in Figs. 5 and 6. It will be seen that, at the pressures used, oxidation of the former takes place at a measurable rate. In run (1) the pressure–time curve gradually decreases in slope as the oxygen accumulates in the reaction vessel; on stopping the oxygen after 20 mins. the contraction accompanying the reaction is clearly seen. In (2), at a higher pressure of trimethylstibine the *p*–*t* curve acquires a negative slope after about 8 mins. owing to the greater rate of reaction. The results for triethylstibine are quite different. On admitting oxygen even to low pressures of this alkyl, only a small initial rise in pressure is obtained, this soon giving way to a steady contraction (Fig. 6). At first sight this would appear to indicate a more rapid reaction with this alkyl. However, this is not necessarily so, since the cause of the reactions and the nature of the products might be different in the two cases. To test this point, a run was carried out with triethylstibine, in which the oxygen was cut off before reaching the reversal point (Curve 4, Fig. 6). Practically no further change in pressure occurred, showing that the stationary concentration of oxygen during the run must have been very small. This is in marked contrast to the result of a similar experiment with trimethylstibine (Curve 1, Fig. 5) and shows decisively that the rate of oxidation is much greater in the case of the ethyl compound. The reactions occurring during oxidation are probably complex. For instance, Dyke and Jones (*J.*, 1930, 1921) reported

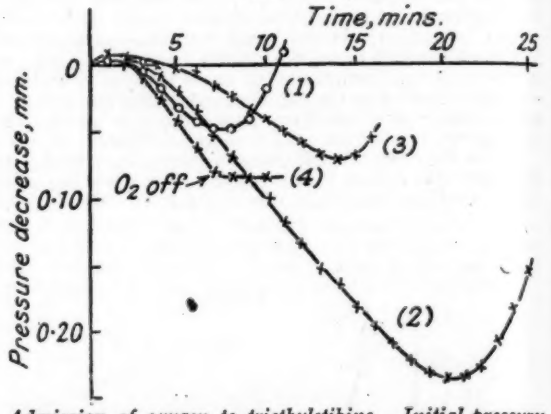
that atmospheric oxidation of the higher antimony alkyls produced a mixture of R_2SbO,Sb_2O_3, and R_3SbO. In the present experiments no attempt was made to carry out a detailed analysis of the products. The oxidation of triethylstibine in the runs described above produced no gas which was not condensable in liquid air. The products had a strong smell of acetaldehyde, and gave a positive Schiff test for this. They appeared to mix completely with water, giving a faintly acid solution, and may have contained $SbEt_2O$ or $SbEtO(OH)_2$.

FIG. 5.



Initial pressures of $SbMe_3$ *(mm.):* (1) 0·49, (2) 0·89. *Rate of entry of* O_2: 0·03 *mm./min.*

FIG. 6.



Admission of oxygen to triethylstibine. Initial pressures of $SbEt_3$ *(mm.):* (1) 0·24, (2) 0·56, (3) 0·44, (4) 0·60. *Rate of entry of* O_2: 0·033 *mm./min.*

DISCUSSION.

1. *Kinetics.*—Since the homogeneous (explosive) oxidation of trimethylboron is subject to inhibition by boron trifluoride–water mixtures, it may be inferred that the oxidation is a chain process. This will be true whether the inhibitor functions in the gas phase or on the surface. It appears, however (p. 697), that the former is more probable. As mentioned on p. 698, the fact that moderate pressures of inert gas have no effect in the reaction rate suggests that chains begin and end on the walls under the conditions of the low-pressure experiments.

As in Part II, we may consider the general reaction scheme represented by equations (I)—(VI) :

Initiation (wall) :	$BMe_3 + O_2 \longrightarrow A +$	(I)
Chain :	$A + BMe_3 \longrightarrow B +$	(II)
	$B + O_2 \longrightarrow BMe_3O_2 + A$	(III)
Chain ending (wall) :	$A \longrightarrow$ wall	(IV)
	$B \longrightarrow$ wall	(V)
Branching :	$B + O_2 + BMe_3 \longrightarrow A + B +$	(VI)

Neglecting the consumption of BMe_3 in (I) and (VI), this gives for the rate of reaction :

$$-\frac{d[BMe_3]}{dt} = k_1 f\{[BMe_3],[O_2]\} \frac{k_2k_3[BMe_3][O_2]}{k_3k_5[BMe_3] + k_3k_4[O_2] + k_4k_5 - k_2k_6[BMe_3]^2[O_2]} \quad . \quad . \quad . \quad (4)$$

where $k_1f\{[BMe_3],[O_2]\}$ is the rate at which the A centres formed by (I) leave the surface. If $k_1f\{[BMe_3],[O_2]\} = k_1[BMe_3][O_2]$, then on putting $k_4 = 0$ in (4) we obtain :

$$-\frac{d[BMe_3]}{dt} = \frac{k_1k_3[BMe_3][O_2]^2}{k_5 - k_6[BMe_3][O_2]} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

which agrees with the experimental observation at low pressures, when the second term of the denominator is negligible in comparison to the first. Sufficient experimental data are not available to enable a comparison to be made with (5) at higher pressures.

The above scheme is similar to that given in Part II for the zinc alkyls, the differences being (*a*) the chain-breaking reaction is the destruction of " B " and not " A " at the walls, (*b*) a different form of expression is used for f, and (*c*) since BMe_3O_2 is the final product there is no need to include a reaction such as (VII), Part II. As with the zinc alkyls, we may obtain a radical chain by writing O and BMe_2O for A and B respectively, or an energy chain if we assume $A = BMe_3O_2^*$ and $B = BMe_3^*$.

A further possibility is that the initial encounter between the alkyls and oxygen produces $O_2 \rightarrow BMe_3$, which then reacts with BMe_3 to give $2BMe_2OMe$, probably in an excited state. The scheme then follows

equations (II), (III), (IV), (VI), with $A \equiv O_2 \rightarrow BMe_2 \cdot OMe$ and $B \equiv BMe_2 \cdot OMe$, and leads to an expression for the rate of reaction essentially the same as (5).

2. *Reaction below Ignition Limit.*—The zinc, boron, and antimony alkyls studied in these papers react rapidly at pressures considerably below the ignition limits. With the ethyl and the propyl derivatives the reactions are in fact always too fast to be readily measurable. In this respect these reactions differ markedly from many other oxidations, *e.g.*, those of hydrogen, phosphorus, phosphine, triethylphosphine (Semenoff, "Chemical Kinetics and Chain Reactions," Oxford, 1935) and silane (Emeléus and Stewart, *J.*, 1935, 1182), all of which exhibit an abrupt lower explosion limit, below which reaction is exceedingly slow. This difference is bound up with the nature of the primary chain. The rate of a chain reaction at low pressures may be expressed as $f(c)/(k - \delta)$, where $f(c)$ is a function of the concentration of reactants representing the rate of primary generation of centres, k determines the probability of chain breaking at the walls, and δ is the branching factor, which of course depends on the concentrations of reactants. If $f(c)/k$ is large, then the rate of reaction will be considerable even in the absence of branching. The condition for an isothermal explosion is $\delta = k$, so that it is quite possible in this case to have a fast reaction well below the ignition limit. In other words, the ignition limit will not be a reaction limit. This will usually also be true if a thermal explosion intervenes before $\delta = k$. On the other hand, if $f(c)/k$ is very small, δ will have to be almost equal to k if the rate is to be measurably fast, in which case a further small increase in pressure will normally be sufficient to give $\delta = k$. Thus the ignition limit will also be approximately a reaction limit.

These considerations are therefore consistent with the view that the rate of the primary chain reaction $(f(c)/k)$ is great in the case of the alkyls, and that branching is unimportant except near the ignition limit. In the other oxidations mentioned above the primary chain reaction is sluggish. It may be concluded that normally the range of pressures over which reaction occurs below the lower ignition limit is an indication of the probability of the primary (unbranched) chain reaction, a wide range corresponding to a high probability and *vice versa*. An exception to this will be the cases (unusual at low pressures) in which the branching and termination reactions depend on the pressures of reactants in a similar manner.

3. *The Relative Rates of Oxidation of Methyl and Higher Alkyls.*—The results described in this and the preceding paper show that the methyl compounds of zinc, boron, and antimony oxidise at a much slower rate than the ethyl and *n*-propyl derivatives. In all these oxidations a central atom–carbon bond is broken, and it is to be expected that the rate of reaction will be affected by changes in the bond energy of this link. The only relevant data on these bond energies are those of Dr. L. H. Long (unpublished), which show that the Zn–C bond in dimethylzinc is a few kg.-cals. stronger than that in diethylzinc. This change in bond energy is due to hyperconjugation and is produced by additional resonance in the higher aliphatic radicals according to the ideas first expressed by Wheland (*J. Chem. Physics*, 1934, **2**, 474) and Baker and Nathan (*J.*, 1935, 1844) and developed by Polanyi and his co-workers (see, *e.g.*, Baughan, Evans, and Polanyi, *Trans. Faraday Soc.*, 1941, **37**, 377; Butler and Polanyi, *ibid.*, 1943, **39**, 19). For example, in the ethyl radical, $CH_3 \cdot CH_2 \cdot$ and the three structures of the type $H-\overset{H}{\underset{H}{C}}=CH_2$ contribute, while in *n*-propyl and higher radicals there are probably further resonating structures. As a consequence there may be a fall in the bond energy from CH_3–X to C_2H_5–X provided the increase in resonance energy of the radical is not outweighed by the increasing interaction between the ionic and homopolar states of RX which is due to the resonance of R ions, and which increases from CH_3 to C_2H_5. Such a fall in bond energy has been observed by Butler and Polanyi (*ibid.*) in a series of organic iodides; presumably the same effect is operative in the alkyls of zinc, boron, and antimony. As there is in fact a falling off in the strength of the Zn–C bond as one passes from the methyl to the ethyl, it is likely that there will be a similar effect with the boron and antimony compounds, since the ionic contributions will be smaller in the derivatives of these elements than in those of zinc.

It is noteworthy that the odour of zinc compounds probably gives a qualitative indication of the rapidity with which they oxidise in the air. Thus the methyls have a pungent and characteristic smell, while the higher alkyls are practically odourless. Further, the decrease in spontaneous inflammability which accompanies an increase in molecular weight must be due to the corresponding decrease in vapour pressure.

The investigations described in this and Parts I and II were carried out in the Physical Chemical Laboratory at Cambridge, and our thanks are due to Professor R. G. W. Norrish, F.R.S., for providing the necessary facilities and for contributing many helpful suggestions during the course of the work.

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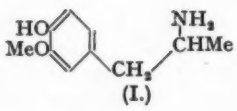
145. *The Synthesis of 3-Methylisoquinolines. Part II.*

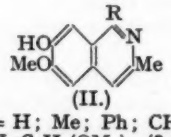
By G. R. CLEMO and J. H. TURNBULL.

The preparation of a series of 3-methyldihydro*iso*quinolines from 4-hydroxy-3-methoxy-β-phenyl*iso*propylamine (I, cf. Part I, *J.*, 1945, 533) is described. These dihydro*iso*quinolines have been converted into *iso*quinolines of type (II), and their 1 : 2 : 3 : 4-tetrahydro-derivatives. One of the type (II) bases is isomeric with papaverine.

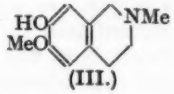
THE value of papaverine as a spasmolytic agent was early recognised by Macht (*J. Pharm. Exp. Ther.*, 1918, **11**, 389) and several papaverine analogues have since been made (Kulz and Hornung, U.S.P. 2,223,373; B.P. 512,560; v. Fodor, *Ber.*, 1943, **76**, 1216; v. Fodor, *Wien. Chem. Ztg.*, 1942, **45**, 241; Scheuing and Walach, D.-R.P. 576,532; Mannich and Falber, *Arch. Pharm.*, 1929, **267**, 601). Recently several dihydro- and tetrahydro-*iso*quinolines have been synthesised and have shown promising pressor, depressor, and convulsant properties (cf. Hjört, *J. Pharm. Exp. Ther.*, 1942, **76**, 64, 71, 252).

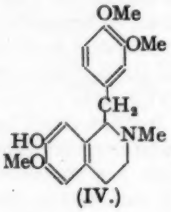
The *iso*quinoline derivatives now described all possess the 4-hydroxy-3-methoxy-β-phenyl*iso*propylamine unit, which may be expected to confer low toxicity on the compounds (cf. Gunn, Gurd, and Sachs, *J. Physiol.*, 1939, **95**, 485). The 7-hydroxy-6-methoxy-1 : 2 : 3 : 4-tetrahydro*iso*quinoline structure is present in a few of the simpler naturally occurring bases, *e.g.*, corypalline (III), codamine (IV), and coclaurine (V), and some of the tetrahydro-bases here described are of interest in their resemblance to these alkaloids.

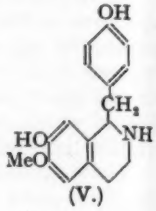

(I.)


(II.)

[R = H; Me; Ph; CH_2Ph; $CH_2{\cdot}C_6H_3(OMe)_2$ (3 : 4)]


(III.)


(IV.)


(V.)

The parent dihydro*iso*quinoline (corresponding to type II, R = H) has been made from the *N*-formyl derivative of the *iso*propylamine (I), after suitably protecting the free hydroxyl group. The most direct route to the required dihydro*iso*quinoline is from the *ON*-diformyl derivative of the amine (I). There are, however, few references in the literature to the preparation of *O*-formyl derivatives, and no satisfactory method of making the *ON*-diformyl*iso*propylamine has, so far, been found. The method of Einhorn and Hollandt (*Annalen*, 1898, **301**, 113) could not be applied to the *iso*propylamine, while refluxing the amine with formic acid gave only the amine monoformate.

Attempts to prepare the dihydro*iso*quinoline from the *N*-formyl-*O*-acetyl*iso*propylamine failed. The *N*-formyl*iso*propylamine was obtained by heating the amine formate (cf. Decker, Kropp, Hoyer, and Becker, *Annalen*, 1913, **395**, 282), but on acetylation gummy products of doubtful purity were obtained. These gums could not be cyclised satisfactorily. The formyl group is probably involved in side-reactions during acetylation of the phenolic hydroxyl (cf. Nef, *Annalen*, 1892, **270**, 278; Pictet and Crépieux, *Jahresber.*, 1888, 1693; Pictet, *Ber.*, 1890, **23**, 3013; Friedmann and Backeberg, *J.*, 1938, 469).

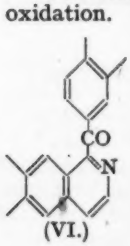
Attention was finally turned to the *O*-benzoyl-*N*-formyl*iso*propylamine. This might be made by formylation of the amino-group in the *O*-benzoyl derivative of the *iso*propylamine (I). The basic monobenzoate of (I), however, could not be obtained, as treatment of 4-hydroxy-3-methoxy-β-phenyl*iso*propylamine hydrochloride with benzoyl chloride (cf. Mannich and Merz, *Arch. Pharm.*, 1927, **265**, 26) always resulted in *N*-benzoylation to give only non-basic products.

The required *O*-benzoyl-*N*-formyl*iso*propylamine was eventually made by benzoylation of the *N*-formyl derivative under Schotten–Baumann conditions. Cyclisation of the amide, however, gave only a small yield of the dihydro*iso*quinoline. Other workers have reported poor yields in similar ring closures (cf. Decker and Becker, *Annalen*, 1911, **382**, 369; Späth, Berger, and Kuntara, *Ber.*, 1930, **63**, 134).

The 1-phenyldihydro*iso*quinolines were obtained from the *ON*-dibenzoyl derivative of the base (I) using the usual modified Bischler–Napieralski method.

The 1-benzyldihydro*iso*quinolines were prepared similarly by cyclising the *ON*-bisphenylacetyl*iso*propylamine. They formed stable salts, but the free bases melted indefinitely and rapidly underwent oxidation in air to yield well-defined crystalline bases of sharp m. p. These bases formed yellow salts, and gave a Prussian blue coloration on boiling with acetic anhydride. They are evidently 1-benzoyldihydro*iso*quinolines resembling those investigated by Buck, Haworth, and Perkin (*J.*, 1924, 2176).

The 1-benzyl bases were stable to warm 10% alcoholic potassium hydroxide, and underwent no appreciable oxidation. This result contrasts with the findings of Buck and co-workers (*loc. cit.*) who were able simultaneously to oxidise the dihydro*iso*quinoline ring and the 1-benzyl group to give a papaveraldine type (VI).


(VI.)

The 1-(3 : 4-dimethoxybenzyl)dihydro*iso*quinolines are more susceptible to atmospheric oxidation than the 1-benzyl compounds. Homoveratric acid (Bide and Wilkinson, *J. Soc. Chem. Ind.*, 1945, **64**, 84) was converted into the acid chloride, which was used to make the *ON*-dihomoveratroyl derivative of the amine (I). The amide was cyclised in a hydrogen atmosphere. The unstable 1-(3 : 4-dimethoxybenzyl) base was isolated as a very sparingly soluble perchlorate. The stable hydrochloride of the base was obtained by decomposition of the perchlorate with ammonia followed by conversion of the free base into the hydrochloride.

The *iso*quinolines (II, R = H; Me; Ph; CH_2Ph) were prepared from the dihydro-bases by dehydrogenation with palladium black (cf. Späth and Polgar, *Sitzungsber.*, 1928, **137**, 1142). One of the *iso*quinolines

made by this method (II, R = Me) has been prepared by v. Fodor from eugenol ψ-nitrosite (*Ber.*, 1943, **76**, 1216).

Attempts to dehydrogenate the 1-(3 : 4-dimethoxybenzyl)dihydro*iso*quinoline were not promising, because of the unstable nature of the dihydro-base. Reduction of the dihydro-base, however, gave a stable tetrahydro-compound, and this was successfully dehydrogenated to give the base [II; R = $CH_2 \cdot C_6H_3(OMe)_2$ (3 : 4)]. This base is of interest in its resemblance to papaverine, with which it is isomeric. Both bases give a violet coloration on warming with sulphuric acid; with Marquis' reagent (Warren, *J. Amer. Chem. Soc.*, 1915, **37**, 2402) papaverine gives a rose pink, whereas the isomer gives a slowly developed light red.

Reduction of the dihydro*iso*quinolines to the tetrahydro-bases was readily effected in aqueous solutions of the hydrochlorides using hydrogen in the presence of palladised charcoal, or Adams's catalyst.

Experimental.

4-Hydroxy-3-methoxy-β-phenylisopropylamine Formate.—4-Hydroxy-3-methoxy-β-phenyl*iso*propylamine (0·48 g.) was dissolved in formic acid (50%, 2 c.c.), and the solution evaporated to dryness under reduced pressure on the water-bath. The residue crystallised from acetone–methanol in pinkish white nodules (0·4 g., m. p. 152—154°). It is readily soluble in water, and on basifying with potassium carbonate its solution deposits a solid, m. p. 156—157·5° not depressed by admixture with an authentic specimen of 4-hydroxy-3-methoxy-β-phenyl*iso*propylamine. The formate was dried in a vacuum at 80° for analysis (Found: N, 6·2. $C_{10}H_{15}O_3N,CH_2O_2$ requires N, 6·2%).

Formo-4-hydroxy-3-methoxy-β-phenylisopropylamide.—The crude syrupy formate obtained above was heated at 145° for 4 hours, and the product extracted with boiling benzene (20 c.c.). On keeping, small white rosettes (0·44 g., m. p. 92—94°) were deposited which recrystallised from benzene in silky needles, m. p. 96—98°. The *amide* was somewhat soluble in water, the solution giving a blue coloration with ferric chloride (Found: N, 6·5. $C_{11}H_{15}O_3N$ requires N, 6·7%).

Benzoylation of 4-Hydroxy-3-methoxy-β-phenylisopropylamine Hydrochloride.—The foregoing compound (0·45 g.) was suspended in xylene (6 c.c.) and benzoyl chloride (0·37 g.) added. The mixture was refluxed for 2 hours with stirring and then cooled. The xylene layer was decanted from the oily residue which was repeatedly extracted with hot water, leaving a pasty solid (*A*). The aqueous extracts were extracted with ether and basified with dilute sodium hydroxide solution, but no 4-benzoxy-3-methoxy-β-phenyl*iso*propylamine could be isolated. The solution was then acidified (Congo-red) with hydrochloric acid and saturated with sodium carbonate; 4-hydroxy-3-methoxy-β-phenyl*iso*propylamine (80 mg.) was then deposited. The solid (*A*) was crystallised from dilute methanol and extracted with cold dilute sodium hydroxide solution, and the extracts were acidified with hydrochloric acid yielding a white solid (0·2 g., m. p. 133—136°) which recrystallised from dilute alcohol to give *benzo-4-hydroxy-3-methoxy-β-phenylisopropylamide* as clusters of delicate white needles, m. p. 136—137° (Found: N, 4·9. $C_{17}H_{19}O_3N$ requires N, 4·9%).

On the addition of benzoyl chloride to the amide dissolved in cold dilute sodium hydroxide solution a white solid separated, which recrystallised from dilute alcohol to give benzo-4-benzoxy-3-methoxy-β-phenyl*iso*propylamide as clusters of small white needles, m. p. 165—166·5°, undepressed by admixture with an authentic specimen.

Formo-4-benzoxy-3-methoxy-β-phenylisopropylamide.—Formo-4-hydroxy-3-methoxy-β-phenyl*iso*propylamide (0·7 g.) was dissolved in ice-cold 0·5N-sodium hydroxide solution (35 c.c.), and a solution of benzoyl chloride (0·6 g.) in ether (6 c.c.) was added dropwise with stirring during 40 minutes. The pasty material which separated was taken up in chloroform, shaken with dilute hydrochloric acid, and then with water. The chloroform solution was dried (Na_2SO_4) the chloroform removed, and the gummy residue treated with light petroleum until crystalline. The solid obtained (0·5 g., m. p. 73—83°) was recrystallised first from benzene–light petroleum and finally from dilute alcohol, giving rosettes of minute white needles (0·3 g.), m. p. 98—99° (Found: N, 4·7. $C_{18}H_{19}O_4N$ requires N, 4·5%).

7-Benzoxy-6-methoxy-3-methyl-3 : 4-dihydroisoquinoline.—The foregoing compound (0·4 g.) was dissolved in chloroform (4 c.c.), phosphoryl chloride (0·8 c.c.) added, and the solution gently refluxed for one hour. The chloroform and excess of phosphoryl chloride were removed under reduced pressure, and the residue was extracted with hot dilute acetic acid. Much reddish material remained undissolved. The acid extracts were shaken with benzene, cooled, and basified with potassium carbonate. The base was isolated by extraction with chloroform, and converted into the hydrochloride which crystallised from acetone in white needles (94 mg.). The free *base*, liberated from an aqueous solution of the hydrochloride by potassium carbonate, slowly crystallised to a white solid (80 mg., m. p. 123—126°), and was recrystallised twice from light petroleum (b. p. 100—120°) to form clusters of colourless needles, m. p. 125—126°. The *picrate*, obtained by mixing aqueous solutions of the above hydrochloride and potassium picrate, recrystallised from methanol in long pale-yellow silky needles, m. p. 202—203° (Found: C, 55·6; H, 4·0. $C_{18}H_{17}O_3N,C_6H_3O_7N_3$ requires C, 55·1; H, 3·9%).

7-Hydroxy-6-methoxy-3-methyl-3 : 4-dihydroisoquinoline.—The foregoing hydrochloride (90 mg.) was dissolved in alcohol (1 c.c.) and 10% sodium hydroxide solution (2 c.c.) was added. The mixture was heated in the water-bath for one hour, and acidified with hydrochloric acid; benzoic acid (15 mg., m. p. 119—121°) then separated. The solution was basified with potassium carbonate, and the liberated base was isolated by extraction with chloroform and treated with light petroleum until crystalline. The white solid (40 mg., m. p. 141—143°) was somewhat soluble in water, giving a yellow solution. It crystallised from benzene (charcoal) in large colourless plates, falling to a white powder at 100° (Found: C, 68·8; H, 6·8. $C_{11}H_{13}O_3N$ requires C, 69·1; H, 6·9%).

Benzo-4-benzoxy-3-methoxy-β-phenylisopropylamide.—4-Hydroxy-3-methoxy-β-phenyl*iso*propylamine (0·5 g.) was dissolved in 0·5N-sodium hydroxide solution (40 c.c.), a solution of benzoyl chloride (0·94 g.) in benzene (3 c.c.) was added dropwise with stirring, and the white solid which separated was collected and recrystallised twice from dilute alcohol, giving the *amide* as clusters of small white needles (0·5 g.), m. p. 165—167° (Found: C, 74·2; H, 5·8. $C_{24}H_{22}O_4N$ requires C, 74·1; H, 6·0%).

7-Benzoxy-6-methoxy-1-phenyl-3-methyl-3 : 4-dihydroisoquinoline.—The foregoing amide (0·5 g.) was dissolved in toluene (2·7 c.c.) and phosphoryl chloride (0·8 c.c.) was added. The mixture was refluxed for one hour, cooled, light petroleum added, the precipitated gum washed with light petroleum, and volatile material removed. The residue was dissolved in hot water, and the cooled solution was extracted once with ether, and basified with ammonium hydroxide. The white solid which separated (0·45 g., m. p. 156—157·5°) crystallised from dilute alcohol in glistening white leaflets, m. p. 157—158·5° (Found: C, 77·9; H, 5·7. $C_{24}H_{21}O_3N$ requires C, 77·6; H, 5·7%). The *picrate* crystallised from alcohol in clusters of yellow needles, m. p. 181—182·5° (Found: N, 9·8. $C_{24}H_{21}O_3N,C_6H_3O_7N_3$ requires N, 9·4%). The *methiodide*, formed by refluxing the base for 2 hours with methyl iodide in acetone solution, crystallised from acetone in bright yellow prisms, m. p. 215° (decomp.) (Found: C, 58·3; H, 4·3. $C_{24}H_{21}O_3N,CH_3I$ requires C, 58·5; H, 4·7%). The hydrochloride of the base crystallised from acetone–methanol in clusters of white glistening prisms, m. p. 174—175° (decomp.).

7-Hydroxy-6-methoxy-1-phenyl-3-methyl-3 : 4-dihydroisoquinoline Hydrochloride.—The foregoing base (0·8 g.) was dissolved in concentrated hydrochloric acid (7·5 c.c.) and water (7·5 c.c.); the solution was heated for 4 hours on the water-bath, cooled, filtered from benzoic acid (0·2 g.), and evaporated. The gummy residue crystallised from acetone–methanol, gave the *hydrochloride* in stout golden yellow prisms (0·6 g.), m. p. 206—207° (decomp.) (Found: N, 4·4. $C_{17}H_{17}O_2N$,HCl requires N, 4·6%).

The free *base*, liberated from an aqueous solution of the hydrochloride, crystallised from ethyl acetate (charcoal) in rosettes of creamy-white small needles, m. p. 103—105° (Found: C, 75·7; H, 6·6. $C_{17}H_{17}O_2N$ requires C, 76·3; H, 6·4%). The picrate crystallised from alcohol in bright-yellow prisms, m. p. 223—225° (decomp.).

Phenylaceto-4-phenylacetoxy-3-methoxy-β-phenylisopropylamide.—4-Hydroxy-3-methoxy-β-phenylisopropylamine (0·3 g.) was dissolved in 0·5N-sodium hydroxide solution, and a solution of phenylacetyl chloride (1·1 g.) in benzene (3·3 c.c.) was dropped in during one hour with stirring. The crude amide obtained was recrystallised from dilute alcohol (0·45 g., m. p. 113—115·5°). A portion after further recrystallisation formed a fluffy mass of small white needles, m. p. 116—117° (Found: N, 3·4. $C_{26}H_{27}O_4N$ requires N, 3·4%).

7-Phenylacetoxy-6-methoxy-1-benzyl-3-methyl-3 : 4-dihydroisoquinoline Hydrochloride.—The foregoing amide (1·2 g.) was dissolved in chloroform (12 c.c.); phosphoryl chloride (1·8 c.c.) was added, and the solution refluxed for one hour. The chloroform was removed under reduced pressure, the residue dissolved in ice-cold methanol, and water added to incipient cloudiness. The cool mixture was basified with potassium carbonate; the base then separated as a pale yellow oil. It was rapidly taken up in warm chloroform, the extract dried (Na_2SO_4), and the chloroform removed. The residual gum was rubbed with a slight excess of ice-cold dilute hydrochloric acid; a solid separated (0·7 g., m. p. 185—190°) and was recrystallised twice from acetone–methanol to give a mass of small white needles (0·42 g.), m. p. 207—208° (decomp.) (Found: C, 71·2; H, 5·7. $C_{26}H_{25}O_3N$,HCl requires C, 71·6; H, 6·0%). The *picrate* of the base, prepared directly from a methanolic solution of the hydrochloride, crystallised from alcohol in long glistening yellow needles, m. p. 165·5—166·5° (Found: C, 61·1; H, 4·5. $C_{26}H_{25}O_3N,C_6H_3O_7N_3$ requires C, 60·9; H, 4·3%).

The free *base*, liberated from a dilute methanolic solution of the hydrochloride by the addition of potassium carbonate, crystallised from dilute alcohol in long colourless prisms and was dried in a vacuum. On standing in the air it became sticky and melted indefinitely between 60° and 70° (Found: C, 75·0; H, 6·6. $C_{26}H_{25}O_3N,H_2O$ requires C, 74·8; H, 6·5%).

7-Phenylacetoxy-6-methoxy-1-benzoyl-3-methyl-3 : 4-dihydroisoquinoline.—The hydrochloride of the foregoing base (220 mg.) was decomposed as usual, the unstable base dissolved in methanol (3 c.c.), allowed to stand in an open vessel at room temperature for 14 days with frequent additions of solvent and evaporated to dryness under reduced pressure; the gummy residue crystallised from dilute methanol to give a creamy-white solid (40 mg., m. p. 136—141°) which recrystallised from dilute methanol in colourless glistening leaflets, m. p. 144—145° (Found: C, 75·4; H, 5·5. $C_{26}H_{23}O_4N$ requires C, 75·5; H, 5·6%). It dissolved in sulphuric acid to give a yellow solution which turned pale orange on warming. Its solution in warm acetic anhydride slowly developed a Prussian-blue colour on boiling.

7-Hydroxy-6-methoxy-1-benzyl-3-methyl-3 : 4-dihydroisoquinoline Hydrochloride.—7-Phenylacetoxy-6-methoxy-1-benzyl-3-methyl-3 : 4-dihydroisoquinoline hydrochloride (0·7 g.) was mixed with water (12 c.c.) and concentrated hydrochloric acid (12 c.c.), heated for two hours in the water-bath, and evaporated to dryness. The residual gum crystallised from acetone as a white solid [0·5 g., m. p. 215° (decomp.)] which recrystallised from acetone–methanol in glistening faintly greenish prisms, m. p. 219—221° (decomp.) (Found: C, 67·4; H, 6·1. $C_{18}H_{19}O_2N$,HCl requires C, 68·0; H, 6·3%). The *picrolonate* of the base, prepared by mixing aqueous solutions of potassium picrolonate and the hydrochloride, crystallised from alcohol in buff-yellow needles, m. p. 233—234° (Found: C, 61·9; H, 4·7. $C_{18}H_{19}O_2N,C_{10}H_8O_5N_4$ requires C, 61·6; H, 5·0%).

The free base crystallised from dilute methanol in clusters of long, pale yellow, silky needles (m. p. 98—107°), which rapidly underwent oxidation in the air.

7-Hydroxy-6-methoxy-1-benzoyl-3-methyl-3 : 4-dihydroisoquinoline.—The foregoing free base from the hydrochloride (0·25 g.) was dissolved in methanol (3 c.c.) and the solution allowed to oxidise as above. The crystalline material which was slowly deposited was rubbed with dilute methanol giving a solid (124 mg., m. p. 160—163°) which was recrystallised once from benzene–light petroleum (b. p. 100—120°) and finally from dilute methanol when it formed clusters of pale yellow prismatic needles, m. p. 164—165° (Found: C, 73·6; H, 6·0. $C_{18}H_{17}O_2N$ requires C, 73·2; H, 5·8%). A trace of the substance gave a colourless solution in warm acetic anhydride and slowly developed a Prussian-blue coloration on boiling.

The *hydrochloride* crystallised from acetone–methanol in rosettes of small pale yellow needles, m. p. 200—201° (decomp.), which were readily soluble in cold water giving a bright yellow solution (Found: C, 65·9; H, 5·1. $C_{18}H_{17}O_2N$,HCl requires C, 65·3; H, 5·4%).

Homoveratro-4-homoveratroyloxy-3-methoxy-β-phenylisopropylamide.—4-Hydroxy-3-methoxy-β-phenylisopropylamine (0·3 g.) was dissolved in 0·5N-sodium hydroxide solution (30 c.c.) and homoveratroyl chloride (0·85 g.) in benzene (3·5 c.c.) was dropped in with stirring. The amide (0·65 g.), a gum, was obtained by extraction with chloroform.

7-Homoveratroyloxy-6-methoxy-1-veratryl-3-methyl-3 : 4-dihydroisoquinoline Perchlorate.—The foregoing crude amide (0·6 g.) was dissolved in chloroform (8 c.c.), phosphoryl chloride (1 c.c.) added, and air swept out of the apparatus by a current of hydrogen. The solution was gently refluxed in a stream of hydrogen for one hour, cooled, and shaken with potassium bicarbonate solution until alkaline. The chloroform layer was then run off and evaporated under reduced pressure at 30° in a stream of hydrogen. The gummy residue was immediately extracted with hot dilute acetic acid (40 c.c.), and the extract shaken with warm benzene and finally with ether. The acid solution was cooled, and a slight excess of dilute perchloric acid added drop by drop. The bulky precipitate was collected and recrystallised from acetic acid giving a pale yellow solid (0·34 g., m. p. 207—209°) which recrystallised from acetic acid (charcoal) in a mass of creamy-white minute needles, m. p. 209—210° (Found: C, 57·8; H, 5·8. $C_{30}H_{33}O_7N,HClO_4$ requires C, 58·1; H, 5·5%). The *picrolonate*, prepared directly from a solution of the perchlorate in hot dioxan, crystallised from alcohol as a ginger-brown microcrystalline powder, m. p. 190—191·5° (Found: C, 61·1; H, 5·8. $C_{30}H_{33}O_7N,C_{10}H_8O_5N_4$ requires C, 61·2; H, 5·3%).

The *hydrochloride* was prepared by suspending the foregoing perchlorate (300 mg.) in benzene, and passing in ammonia till the solid had dissolved. The mixture was filtered at once, concentrated as above, cooled, and hydrogen chloride passed in. The gummy hydrochloride was crystallised from acetone–methanol; 190 mg., m. p. 201° (decomp.). It was freed from traces of ammonium perchlorate by washing with cold water, and was finally recrystallised from acetone–methanol, giving a fluffy mass of small white needles, m. p. 201° (decomp.) (Found: C, 64·0; H, 5·9. $C_{30}H_{33}O_7N$,HCl requires C, 64·7; H, 6·1%).

7-Hydroxy-6-methoxy-1-veratryl-3-methyl-3 : 4-dihydroisoquinoline Hydrochloride.—The foregoing hydrochloride (80 mg.) was mixed with water (1·5 c.c.) and concentrated hydrochloric acid (1·5 c.c.), and heated for two hours on the water-bath. The *hydrochloride*, isolated in the usual way, crystallised on treatment with acetone to give a creamy-white solid [52 mg., m. p. 210—211°, decomp.)] which recrystallised from acetone–methanol in small, very faintly yellow needles (46 mg.), m. p. 210—211° (decomp.) (Found: C, 63·5; H, 6·1. $C_{20}H_{23}O_4N$,HCl requires C, 63·5; H, 6·1%).

The *picrolonate*, prepared as above from the hydrochloride, crystallised from alcohol as clusters of orange-yellow prisms, m. p. 178—179° (Found: C, 59·4; H, 5·3. $C_{20}H_{23}O_4N,C_{10}H_8O_8N_4$ requires C, 59·5; H, 5·2%).

7-Hydroxy-6-methoxy-1 : 3-dimethylisoquinoline.—7-Acetoxy-6-methoxy-1 : 3-dimethyl-3 : 4-dihydroisoquinoline (0·3 g.) and palladium black (0·14 g., prepared according to Willstätter, *Ber.*, 1921, **54**, 123) were heated to 175° in a sublimation tube during 10 minutes, and maintained at 173—175° for a further 30 minutes. The temperature was then lowered to 120—130° and the pressure reduced to 2 mm.; a colourless gum then condensed on the upper part of the tube. It crystallised on rubbing with ether to give a white solid (0·13 g.) which was hydrolysed by warming for one hour on the water-bath with water (0·5 c.c.) and concentrated hydrochloric acid (0·5 c.c.). A crystalline hydrochloride slowly separated from which the free base was obtained and crystallised from acetone; 0·1 g., m. p. 181—182° (Fodor records m. p. 175°) (Found: C, 71·0; H, 6·1; N, 6·9. Calc. for $C_{13}H_{13}O_2N$: C, 70·8; H, 6·4; N, 6·9%). The base was somewhat soluble in water, the solution showing a deep green fluorescence at high dilutions. The *picrate* crystallised from alcohol in deep yellow platelets, m. p. 243° (decomp.) (Found: C, 50·3; H, 3·8. $C_{13}H_{13}O_2N,C_6H_3O_7N_3$ requires C, 50·0; H, 3·7%).

7-Benzoxy-6-methoxy-1-phenyl-3-methylisoquinoline.—7-Benzoxy-6-methoxy-1-phenyl-3-methyl-3 : 4-dihydroisoquinoline (0·2 g.) was mixed with palladium black (90 mg.) and heated for 1·5 hours to 170—175°/2 mm. The chloroform extract was converted into the hydrochloride, recrystallised from water and the free *base* obtained as colourless needles from dilute alcohol, 85 mg., m. p. 140—141° (Found: N, 4·1. $C_{24}H_{19}O_2N$ requires N, 3·8%). The picrate crystallised from alcohol in felted masses of small yellow needles, m. p. 210—211°.

7-Hydroxy-6-methoxy-1-phenyl-3-methylisoquinoline.—The foregoing hydrochloride (70 mg., m. p. 187—190°), dissolved in alcohol (1 c.c.), was heated for 3 hours on the water-bath with 10% sodium hydroxide (1·5 c.c.). Excess of alcohol was removed, the product acidified (hydrochloric acid), and the warm solution basified (potassium carbonate). The *base* crystallised on cooling (45 mg., m. p. 181—184°), and recrystallised from toluene (charcoal) in fan-shaped clusters of colourless prisms (35 mg.), m. p. 206—207° (Found: C, 76·7; H, 5·6. $C_{17}H_{15}O_2N$ requires C, 76·9; H, 5·7%). The *picrate* crystallised from alcohol in lemon-yellow prisms, m. p. 227° (Found: C, 56·6; H, 3·6. $C_{17}H_{15}O_2N,C_6H_3O_7N_3$ requires C, 56·0; H, 3·7%).

7-Hydroxy-6-methoxy-1-benzyl-3-methylisoquinoline.—7-Phenylacetoxy-6-methoxy-1-benzyl-3-methyl-3 : 4-dihydroisoquinoline hydrochloride (160 mg.) was decomposed with potassium carbonate in the usual way, and the unstable free base mixed with palladium black (80 mg.). The pressure was reduced to 2 mm., and the temperature raised to 163° during 15 minutes and kept at 163—165° for a further 30 minutes. The dehydrogenated base was converted into the hydrochloride, which was crystallised from acetone, and warmed with 10% sodium hydroxide solution (1 c.c.) for two hours on the water-bath. The crystalline sodium salt which separated was decomposed with hydrochloric acid to give a white solid hydrochloride (23 mg.). The free *base*, liberated from the hydrochloride, crystallised from dilute methanol in colourless plates (15 mg.), m. p. 157—158°, which fell to a white powder on drying at 100°/2 mm. (Found: C, 77·5; H, 6·2. $C_{18}H_{17}O_2N$ requires C, 77·4; H, 6·1%). A dilute aqueous solution of the base showed a deep green fluorescence. The *picrate* recrystallised from dilute methanol in long slender yellow prisms, m. p. 199—200° (Found: C, 57·0; H, 4·0. $C_{18}H_{17}O_2N,C_6H_3O_7N_3$ requires C, 56·7; H, 4·0%).

7-Hydroxy-6-methoxy-1 : 3-dimethyl-1 : 2 : 3 : 4-tetrahydroisoquinoline.—7-Hydroxy-6-methoxy-1 : 3-dimethyl-3 : 4-dihydroisoquinoline (0·1 g.) was dissolved in dilute hydrochloric acid (5 c.c.), a solution of palladium chloride (40 mg.) in dilute hydrochloric (5 c.c.) added, and the mixture shaken with charcoal (0·1 g.) at 40° for 12 hours in hydrogen. The colourless solution was filtered and evaporated; the liberated *base* (170 mg.) crystallised from acetone in colourless leaflets, m. p. 169—170° (Found: C, 69·9; H, 8·2. $C_{12}H_{17}O_2N$ requires C, 69·6; H, 8·3%). The *picrate* crystallised from ethyl acetate–methanol in yellow-orange prisms, m. p. 200—201° (decomp.) (Found: C, 49·8; H, 4·6. $C_{18}H_{17}O_2N,C_6H_3O_7N_3$ requires C, 49·6; H, 4·6%).

7-Hydroxy-6-methoxy-1-phenyl-3-methyl-1 : 2 : 3 : 4-tetrahydroisoquinoline Hydrochloride.—7-Hydroxy-6-methoxy-1-phenyl-3-methyl-3 : 4-dihydroisoquinoline (50 mg.) was hydrogenated in dilute hydrochloric acid solution using palladium chloride (20 mg.) and charcoal as above. The *hydrochloride* of the tetrahydro-base separated as a sparingly soluble white solid [40 mg., m. p. 310° (decomp.)]. It crystallised from methanol–acetone in masses of minute silky needles, m. p. 320° (decomp.) (Found: C, 66·4; H, 6·6. $C_{17}H_{15}O_2N,HCl$ requires C, 66·7; H, 6·6%).

The free *base* crystallised from dilute methanol in clusters of colourless needles, m. p. 142—143·5° (Found: C, 75·5; H, 7·1. $C_{17}H_{19}O_2N$ requires C, 75·7; H, 7·1%).

7-Hydroxy-6-methoxy-1-benzyl-3-methyl-1 : 2 : 3 : 4-tetrahydroisoquinoline Hydrochloride.—7-Hydroxy-6-methoxy-1-benzyl-3-methyl-3 : 4-dihydroisoquinoline hydrochloride (0·1 g.) was dissolved in water (6 c.c.) and shaken with platinum oxide (10 mg.) in hydrogen for 12 hours. The pale yellow solution became colourless. The *hydrochloride* of the tetrahydro-base crystallised from acetone–methanol in small white needles [85 mg., m. p. 243° (decomp.)]. The free *base* recrystallised from light petroleum (b. p. 100—120°) in rosettes of colourless needles, m. p. 118—119° (Found: C, 75·7; H, 7·3. $C_{18}H_{21}O_2N$ requires C, 76·2; H, 7·5%). The picrate crystallised from methanol in bright yellow prisms, m. p. 230—231° (decomp.).

7-Hydroxy-6-methoxy-3-methyl-1 : 2 : 3 : 4-tetrahydroisoquinoline.—7-Hydroxy-6-methoxy-3-methyl-3 : 4-dihydroisoquinoline (43 mg.) was dissolved in 0·5N-hydrochloric acid (10 c.c.) and the mixture shaken for 3 hours in hydrogen with platinum oxide (5 mg.). The colourless solution was evaporated giving a white solid hydrochloride (50 mg., m. p. 285°). The free *base* crystallised from benzene in small white rosettes (38 mg.), m. p. 151—152° (Found: C, 68·5; H, 7·7. $C_{11}H_{15}O_2N$ requires C, 68·4; H, 7·9%).

7-Hydroxy-6-methoxy-1-veratryl-3-methyl-1 : 2 : 3 : 4-tetrahydroisoquinoline.—7-Hydroxy-6-methoxy-1-veratryl-3-methyl-3 : 4-dihydroisoquinoline hydrochloride (68 mg.) was dissolved in water (10 c.c.) and shaken in hydrogen with platinum oxide (8 mg.) for 4 hours. The colourless solution yielded a white solid hydrochloride (54 mg.) which crystallised from dilute hydrochloric acid (1·5 c.c.) in colourless, glistening plates (43 mg.). The free *base* crystallised from dilute methanol in colourless prisms (30 mg.), m. p. 120—121° (Found: C, 69·9; H, 7·5. $C_{20}H_{25}O_4N$ requires C, 69·9; H, 7·3%).

7-Hydroxy-6-methoxy-1-veratryl-3-methylisoquinoline.—The tetrahydro-base (50 mg.) was mixed with palladium black (30 mg.) and the mixture dehydrogenated as in the case of the 1-benzyl compound. The *product*, isolated by extraction with chloroform, recrystallised from benzene (charcoal) as glistening leaflets (30 mg.), m. p. 173—174° (Found: C, 71·3; H, 6·3. $C_{20}H_{21}O_4N$ requires C, 70·8; H, 6·3%).

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146. *The Ionisation of Acridine Bases.*

By Adrien Albert and Reginald Goldacre.

It has recently been claimed that antibacterial activity in the acridine series is associated with those members that exhibit more than 60% of cationic ionization, at pH 7·3 and 37° (Albert, Rubbo, Goldacre, Davey, and Stone, *Brit. J. Exper. Path.*, 1945, **26**, 160). The present paper supplies the chemical part of the evidence for this claim (i) by reporting 95 new ionisation constants, (ii) by discussing the effects of alcohol and of temperature on the ionisation of sparingly soluble bases, and (iii) by demonstrating new correlations between basic strength and structure in the acridine series.

In an earlier paper (Albert and Goldacre, *J.*, 1943, 454), the ionisation of acridine and 22 of its derivatives was discussed, as part of a programme to correlate structure, basicity, and antibacterial activity in this series. The present paper seeks, first, to give a critical interpretation of the figures already reported, and secondly, to report and discuss 95 new values.

The Effect of Alcohol on Ionisation.—For biological purposes it is very important to know the exact pK_a values in water of bases, particularly those which lie in the range pK_a 6—8, as their degree of ionisation at pH 7 varies greatly with a small change in pK_a. Because of their poor solubility, very few acridine compounds can be titrated potentiometrically in water, and hence it is desirable to know to what extent values obtained by titration in 50% ethanol fall short of the value in water. This comparison has been carried out by determining the pK_a values of acridine and the five isomeric aminoacridines both in 50% ethanol (potentiometric titration) and in water (absorptiometry in aqueous buffers; see Experimental Section). It will be seen from Table I that the depression of basic strength by the alcohol (ΔpK_a) ranges from 0·43 to 1·46 units (average 0·77). These figures are somewhat larger than those obtained on pyridine and simple aliphatic and aromatic amines by Mizutani (*Z. physikal. Chem.*, 1925, **118**, 327), who examined 10 bases in 60% methanol, and Hall and Sprinkle (*J. Amer. Chem. Soc.*, 1932, **54**, 3469), who examined 18 bases in 50% ethanol. These authors obtained maximum values of 0·89 and 0·88, and minimum values of 0·30 and 0·26 (average 0·55 and 0·54 respectively).

The ΔpK_a for acridine is the highest ΔpK_a on record and three times as high as the average found by Mizutani and by Hall and Sprinkle, whose bases had moderately high solubilities in both water and alcohol. That this is not an unreasonably high value follows from the work of Kolthoff, Lingane, and Larson (*J. Amer. Chem. Soc.*, 1938, **60**, 2512), who deduced thermodynamically that the ΔpK_a is a function of the distribution coefficients of the different molecular and ionic species involved in the acid–base equilibrium $\Delta pK_a = \log D_{H^+} + \log D_B - \log D_{BH^+}$, where D_X is the distribution coefficient of X between the two solvents.

The acridine bases now examined are much more soluble in alcohol than in water, in contrast with their hydrochlorides which are fairly readily soluble in both solvents. It does not follow that a still more hydrophobic substance than acridine will exhibit a greater depression, for we obtained a depression of only 0·54 for 6 : 7-benzoacridine (unpublished work), but here the extra hydrocarbon ring has developed hydrophobic properties in the hydrochloride, making it much more soluble in benzene than is acridine hydrochloride.

The reality of the large depression obtained for acridine was confirmed by measuring the pH of equimolecular amounts of acridine and its hydrochloride at a total concentration of M/240, using as solvents 50, 40, 30, 20 and 10% ethanol (by volume), which gave pK_a values of 4·14, 4·35, 4·69, 4·98, 5·20, respectively, at 20°. By extrapolation to 0% alcohol, the pK_a value of 5·55 for water is obtained (cf. 5·60 in Table I), a depression of 1·41 units.

Table III provides six other examples (Nos. 10, 14, 45, 46, 47, and 61) for the calculation of ΔpK_a, which varies between 0·41 and 0·9, averaging 0·58 unit.

Table I.

Effect of alcohol on the ionisation of acridines.

No.	Substance.	pK_a * in 50% EtOH at 20° (±0·5°) (potentiometric titration).	Dilution (1/M).	pK_a in H_2O at 20° (±5°) (absorptiometry).	Dilution (1/M).	ΔpK_a.
—	Acridine	4·11	120	5·60	2500	1·49
1	1-Aminoacridine	3·59	120	4·40	3000	0·81
2	2-Aminoacridine	7·61 †	120	8·04	5000	0·43
3	3-Aminoacridine	5·03	120	5·88	6000	0·85
4	4-Aminoacridine	5·50	120	6·04	6000	0·54
5	5-Aminoacridine	9·45 †	120	9·99	2500	0·54

* pK_a is the negative logarithm of the acidity constant $[B][H^+]/[BH^+]$.

† Previously reported (Albert and Goldacre, *loc. cit.*) as pH of half-neutralisation, but now averaged from ten points on the titration curve, as has been done for the other members of this table which have not previously been reported in ethanol.

It is sometimes assumed (Dippy, *Chem. Reviews*, 1939, **25**, 151; Bennett and Glasstone, *J.*, 1935, 1821) that a series preserves the same order of pK_a in dilute alcohols as in water. Although the data of Table I do not contradict this assumption, they do show that the depression of basic strength by alcohol can vary considerably from member to member of a series of isomerides. However, this may be an exceptional series since three different types of amino-group are involved (Albert and Goldacre, *loc. cit.*) and it is unlikely that such

large differences will be encountered where the nature of the amino-group remains unaltered (*e.g.*, the isomeric methoxy-derivatives of 5-aminoacridine, Table III). Some instances where the order of basic strength of fairly closely related amines is reversed by alcohol can be gleaned from curves published by Hall and Sprinkle (*loc. cit.*).

Effect of Temperature on Ionisation.—Hall and Sprinkle (*loc. cit.*), working between 19° and 32°, have shown that, in water, bases become weaker as the temperature rises and that an almost linear relation exists between pK_a and temperature and between pK_a and dpK_a/dT. No coefficients appear to have been determined for bases in 50% ethanol. As these figures were required for the calculation of some of the values of Table III, the pK_a values of a weak and a strong base, *viz.*, acridine and 5-aminoacridine, have been determined at various temperatures in the range 5—40° and are given in Table II. These two bases give temperature coefficients of −0·0083 (−0·0125) and −0·031 (−0·020) pK_a per unit per degree respectively, the values in parentheses being those for bases of the same pK_a determined in water by Hall and Sprinkle. It would seem that temperature coefficients in 50% alcohol are of the same order as those in water.

TABLE II.

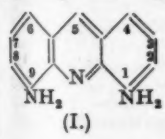
Relation between temperature and pK_a of a weak and a strong acridine base in 50% ethanol (dilution = 120).

Temp.	5°.	10°.	15°.	20°.	25°.	30°.	35°.	37°.	40°.	Temp. coeff.
pK_a, acridine	4·30	4·24	4·14	4·11	4·05	4·01	3·98	3·97	3·93	−0·008
pK_a, 5-aminoacridine ...	9·93	9·75	9·65	9·47	9·29	9·14	8·95	8·90	8·81	−0·031

Effect of Substituents on Ionisation.—The effect of a second amino-group on the ionisation of an aminoacridine should vary according to the position in which it is inserted, because it was shown (Albert and Goldacre, *loc. cit.*) that (i) the primary amino-group in 3- and 4-aminoacridine had a normal aromatic character, (ii) in 1-aminoacridine exerted a base-weakening ortho-effect, and (iii) those in the 2- and the 5-isomeride entered into base-strengthening resonance with the ionised ring nitrogen. That the ring nitrogen is the first to accept a proton in all the monoaminoacridines was shown spectrographically by Craig and Short (*J.*, 1945, 419) and by Turnbull (*ibid.*, p. 441).

It is seen from Table III that the introduction of a second amino-group in the 3- or the 4-position increases the basic strength by a small amount corresponding to the effect that this operation has on acridine itself (cf. Nos. 3, 4, 9, 12, 13, 14). It does not seem to matter whether the primary amino-group originally present was also a normal aromatic group (No. 14) or one resonating with the ionised ring nitrogen (Nos. 9, 12, 13). When the second amino-group is placed in the 2- or the 5-position where it can resonate with the ionised ring nitrogen, a considerably greater increase in basic strength is seen, just as when this operation is carried out on acridine itself (cf. Nos. 2. 5, 9, 10, 11, 12, 13). This increase is very great when the first amino-group is normal (Nos. 9, 12, 13), but even where it is resonant (Nos. 10, 11, 44) the opportunities afforded for extra resonance by the contribution of alternative forms to the resonance hybrid have increased the basic strength substantially more than was effected by a normal amino-group. Just as 2- and 5-aminoacridines are vinylogous amidines, so 2 : 5- and 2 : 8-diaminoacridines are vinylogous guanidines and hence proportionately stronger as bases.

Finally, the base-weakening character of an amino-group inserted in the 1-position is maintained when an amino-group is already present (Nos. 1, 6, 7, 8). In the case of 1 : 9-diaminoacridine (I), the presence of two primary amino-groups ortho to the ring nitrogen have had the effect of excluding the proton from the latter, and Craig (this vol., p. 534) has shown spectrographically that the mono- and di-ions have the protons on the amino-groups and that the low pH of 18N-sulphuric acid is necessary to force a proton on to the ring nitrogen. Actually, the first and second pK_a values of this substance are closer together than those of the other diaminoacridines. The highly weakening effect of the 1-amino-group on the basic strength of 2- and 5-aminoacridine (cf. Nos. 7 and 8) cannot be explained in terms of mere steric hindrance, because the slightly larger methyl group, as in 5-amino-1-methylacridine (No. 23), is base-strengthening. The figures for these two diamines lend additional support to a hypothesis advanced for 1-aminoacridine (Albert and Goldacre, *loc. cit.*) and the analogous 8-aminoquinoline (*idem*, *Nature*, 1944, **153**, 467), *viz.*, that an ortho-effect, akin to hydrogen bonding between the two nitrogen atoms, is interfering with the approach of protons to the ring nitrogen. In all these cases, however, the ring nitrogen is still the first to accept a proton, as the bathochromic nature of the change from base to mono-ion proves (cf. Craig and Short, *loc. cit.*).



(I.)

The effect of alkyl substituents in the acridine nucleus should be to increase the basic strength by a small amount, for they are electron-repelling. Reference to Nos. 15 to 32 (Table III) shows that this effect may vary from 0·09 to 0·59 unit per methyl group, excluding cases where there is a methyl group in the 1-position. In the latter cases, an increase in basic strength is still seen where there is only one methyl group ortho to a ring nitrogen of a highly basic character (5-amino-1-methylacridine, No. 23). However, when both ortho-positions are substituted with methyl groups, or when the ring nitrogen is not highly basic (Nos. 28, 29; 15, 18, 19, 20, and 22), a significant depression of basic strength is seen. No (static) steric hindrance to the approach of protons could explain the depression and elevation of basic strength by the insertion of a methyl group in the 1-position of acridine and 5-aminoacridine respectively, since the access and escape of hydrogen ions would be prevented equally.

1-Amino-9-methylacridine (No. 20) differs from its isomerides in that there are two mono-ions: the normal ion involving the ring nitrogen is red, but it exists in various solvents in equilibrium with different amounts of a colourless form involving the amino-group (see Craig, *loc. cit.*; also Experimental Section).

The phenyl-substituted acridines (Nos. 33—35) exert a base-weakening effect consonant with the electron-attracting nature of this group. In 5-amino-1-phenylacridine a steric effect is probably present also.

The effect of alkoxy-substituents attached to an aromatic structure is not entirely predictable. As with amino-substituents, there is an electrophilic effect (inductive) and an electron-repelling effect (resonant), but with alkoxy-substituents the relative magnitude of the latter effect is not so large. Thus, *m*-, *o*-, and *p*-anisidines (and phenetidines) are weaker than, equal to, and stronger than aniline, respectively, as bases. Likewise, substitution of an alkoxy-group into acridines (Nos. 36—44) causes a small but variable effect on the pK ranging from $-0{\cdot}35$ to $+0{\cdot}24$ unit.

TABLE III.

Ionisation of acridines at 20° (± 0·5°).

(Determined by potentiometry with glass electrode in 50% ethanol unless otherwise stated. Values marked "H_2O" were determined by absorptiometry in water.)

No.	Substance.	Source.	pK_a.*	ΔpK_a.†	Diln.
	Acridine	A	4·11		120
Diaminoacridines.				Acridines.	
6	1 : 9-	B	3·55	−0·04; 1-Amino-	300
7	2 : 9-(= 1 : 8)	C	6·74	−0·87; 2-Amino- +3·15; 1-Amino-	200
8	1 : 5-	B	8·78	−0·67; 5-Amino- +5·19; 1-Amino-	160
9	3 : 5-	D	9·91	+0·46; 5-Amino- +4·88; 3-Amino-	40
10	2 : 5-	E	11·01	+3·40; 2-Amino- +1·56; 5-Amino-	40
	2 : 5- (potentiometry in H_2O)		11·49	+1·50; 5-Amino- (H_2O)	20
11	2 : 8-	F	9·50	+1·89; 2-Amino-	40
12	2 : 7- (= 3 : 8-)	C, G	7·74	+0·13; 2-Amino- +2·71; 3-Amino-	80
13	2 : 6- (= 4 : 8-)	H	8·55	+0·94; 2-Amino- +3·05; 4-Amino-	40
14	3 : 7-	I	5·64	+0·61; 3-Amino-	600
			6·18 (H_2O)	+0·30; 3-Amino- (H_2O)	100,000
C-Alkyl-substituted acridines.					
15	1-Methyl-	J	3·95	−0·16; Acridine	80
16	3-Methyl-	J	4·60	+0·49; Acridine	60
17	5-Methyl-	K	4·70	+0·59; Acridine	60
18	1 : 9-Dimethyl-	A	2·88 } Absorptiometry	−1·23; Acridine	5,000
19	1 : 3 : 4 : 6 : 7 : 9-Hexamethyl-	L	3·0 } in 50% ethanol	−1·1; Acridine	30,000
20	1-*Amino-9-methyl-*	M	3·22	−0·37; 1-Amino-	160
21	3-*Amino-5-methyl-*	M	5·59	+0·57; 3-Amino-	120
22	4-Amino-1-methyl-	G	4·79	−0·71; 4-Amino-	160
23	5-Amino-1-methyl-	N	9·73	+0·28; 5-Amino-	60
24	5-Amino-2-methyl-	N	9·71	+0·26; 5-Amino-	240
25	5-Amino-3-methyl-	N	9·54	+0·09; 5-Amino-	60
26	5-Amino-4-methyl-	N	9·60	+0·15; 5-Amino-	120
27	5-Amino-1 : 3-dimethyl-	N	9·99	+0·54; 5-Amino-	60
28	5-Amino-1 : 9-dimethyl-	N	8·82	−0·63; 5-Amino-	120
29	2 : 8-Diamino-1 : 9-dimethyl-	O	8·51	−0·99; 2 : 8-Diamino-	120
30	2 : 8-Diamino-3 : 7-dimethyl (acridine-yellow)	P	9·7	+0·2; 2 : 8-Diamino-	120
31	2 : 8-Diamino-4 : 6-dimethyl-	G	10·08	+0·58; 2 : 8-Diamino-	40
32	5-Amino-1-ethyl	N	9·66	+0·21; 5-Amino-	120
33	5-Amino-1-phenyl-	N	8·67	−0·78; 5-Amino-	300
34	5-Amino-3-phenyl-	N	9·24	−0·21; 5-Amino-	120
35	2 : 8-Diamino-5-phenyl-3 : 7-dimethyl- (Benzoflavine)	Q	9·11	−0·39; 2 : 8-Diamino-	300
Alkoxy-substituted acridines.					
36	1-Methoxy- (m. p. 134°; lit. gives 130—131°)	K	4·19	+0·08; Acridine	120
37	3-Methoxy-	R	4·27	+0·16; Acridine	120
38	2 : 8-Dimethoxy-	S	5·7	+0·1; Acridine	120
39	5-Amino-1-methoxy-	N	9·38	−0·07; 5-Amino-	120
40	5-Amino-2-methoxy-	N	9·57	+0·12; 5-Amino-	120
41	5-Amino-3-methoxy-	N	9·10	−0·35; 5-Amino-	240
42	5-Amino-4-methoxy-	N	9·69	+0·24; 5-Amino-	240
43	2 : 8-Diamino-3 : 7-dimethoxy	E	9·17	−0·33; 2 : 8-Diamino-	320
44	2 : 5-Diamino-7-ethoxy- (Rivanol)	E	11·04	+0·10; 2 : 5-Diamino-	160

* For definition, see Table I. † That is, the amount by which pK_a exceeds that of the parent substance named.

No.	Substance.	Source.	pK_a.*	ΔpK_a.†	Diln.
Chloro-, cyano-, and nitro-substituted acridines.				Acridines.	
45	5-Chloro-2-amino-	T	5·97	−1·64; 2-Amino-	200
	5-Chloro-2-amino-		6·74 H_2O	−1·30; 2-Amino (H_2O)	100,000
46	7-Chloro-2-amino-	U	6·53	−1·08; 2-Amino-	120
	7-Chloro-2-amino-		6·95 H_2O	−1·09; 2-Amino- (H_2O)	100,000
47	8-Chloro-2-amino-	U	6·85	−0·76; 2-Amino	120
	8-Chloro-2-amino-		7·26 H_2O	−0·78; 2-Amino- (H_2O)	100,000
48	8-Chloro-3-amino-	U	3·98	−1·05; 3-Amino-	240
49	1-Chloro-5-amino-	N	7·82	−1·63; 5-Amino-	120
50	2-Chloro-5-amino-	N	8·33	−1·12; 5-Amino-	80
51	3-Chloro-5-amino-	N	8·31	−1·02; 5-Amino-	120
52	4-Chloro-5-amino-	N	7·89	−1·56; 5-Amino-	200
53	3 : 7-Dichloro-2 : 8-diamino-	G	7·64	−1·86; 2 : 8-Diamino-	400
54	2-Chloro-5-amino-7-methoxy-	V	8·01	−1·44; 5-Amino-	1,000
55	5-Amino-3-cyano-	N	7·46	−1·99; 5-Amino-	240
56	1-Nitro-	D	3·0	−1·1; Acridine	375
57	1-Nitro-5-amino-	N	7·34	−2·11; 5-Amino-	240
58	2-Nitro-5-amino-	E	7·30	−2·15; 5-Amino-	300
59	3-Nitro-5-amino-	D	7·3	−2·1; 5-Amino-	60
60	4-Nitro-5-amino-	N	6·95	−2·50; 5-Amino-	150
61	2-Nitro-5-amino-7-ethoxy-	E	6·6	−2·9; 5-Amino-	1,000
	2-Nitro-5-amino-7-ethoxy-		7·5 H_2O	−2·5; 5-Amino- (H_2O)	50,000
N-Alkyl-substituted acridines.					
62	2-Dimethylamino-	G	7·80	+0·19; 2-Amino-	120
63	2 : 8-Bisdimethylamino (Acridine orange)	W	10·04	+0·54; 2 : 8-Diamino-	160
64	7-Amino-2-dimethylamino-	G	8·02	+0·28; 2 : 7-Diamino-	80
65	5-Dimethylamino-	D	7·53	−1·92; 5-Amino-	40
66	5-Methylamino-	D	9·77	+0·27; 5-Amino-	40
67	5-Butylamino-	V	9·35	−0·10; 5-Amino-	40
68	5-Heptylamino-	V	9·35	−0·10; 5-Amino-	40
69	5-Dodecylamino-	V	9·1	−0·4; 5-Amino-	40
70	5-Hexadecylamino-	V	8·7	−0·8; 5-Amino-	500
71	5-*cyclo*Hexylamino-	V	8·78	−0·67; 5-Amino-	40
72	5-Phenylamino-	D	7·01	−2·44; 5-Amino-	240
73	5-(β-Hydroxyethyl)amino-	N	8·77	−0·68; 5-Amino-	200
74	5-(β-5′-Acridylamino)ethylamino- (*i.e.*, bisacridylethylenediamine)	N	8·52; $pK_2 = 6·92$	−1·0; 5-Amino-	1,200
75	Benzylideneamino-	D	3·37	−0·22; 1-Amino-	400
Miscellaneous acridines.					
76	3-*Aminomethyl*-	M	8·74; $pK_2 = 2·1$	+3·71; 3-Amino-	100
77	5-β-Aminoethyl-	X	8·57; $pK_2 = 3·95$	−0·88; 5-Amino-	300
78	5-*p*-Dimethylaminophenyl-	Y	4·4		3,000
79	2-Amino-5-*p*-aminophenyl- ("Phosphine")	Z	7·71	+0·10; 2-Amino-	120
80	5-*p*-Aminostyryl-	AA	5·10		1,000
81	5-*m*-Aminostyryl-	AA	4·43		600
82	5-*p*-Dimethylaminostyryl-	AA	3·07		1,200
83	1 : 2 : 3 : 4-Tetrahydro-	BB	5·07	+0·96; Acridine	120
84	5-Amino-1 : 2 : 3 : 4-tetrahydro-	N	9·40	−0·05; 5-Amino-	60
85	3-Aminoacridan	D	4·72	−0·31; 3-Amino-	80

* For definition, see Table I. † That is, the amount by which pK_a exceeds that of the parent substance named.

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The effect of chloro-, cyano-, and nitro-substituents, because of their strong electron-attracting character, is to diminish the basic strength of acridines very considerably. Among the monochloro-derivatives (Nos. 45—54) a depression of −0·76 to −1·64 units is observed, among the nitro-derivatives (Nos. 56—61) from −1·1—−2·9, and the cyano-derivative (No. 55) has a depression of −1·99 units. It is noteworthy that the marked differences (*e.g.*, +2·8 units) between the basic strengths of isomeric nitroanilines do not occur here because the peculiar resonance forms of *o*- and *p*-nitroanilines have no close representatives in the present compounds.

The effect of *N*-methyl substitution on the basic strength of aminoacridines is in general similar to its effect on that of aromatic amines which Hall and Sprinkle found (*loc. cit.*) to increase by 0·2 unit for each methyl group inserted (see Nos. 62, 63, 64, 66). As the amines under consideration are all derivatives of 2- and 5-aminoacridine, which owe their high basic strength to ionic resonance, it seemed likely that alkylation might so change the equivalence of the resonance forms that the basic strength would be seriously altered (cf. guanidine; Pauling, " Nature of the Chemical Bond," New York, 1942, p. 213). The results suggest that equivalence has not been seriously disturbed.

5-Dimethylaminoacridine (No. 65) shows a large depression of basic strength, indicating that ionic resonance has been diminished by steric interference between a methyl group and a hydrogen atom in the 4- or 6-position. This overlap of covalent radii is critical because a very small decrease in the distance, as in 5-amino-4-methylacridine (No. 26) or (through bending of the $N^{-}C^{5}$ bond) in 5-methylaminoacridine (No. 66), prevents this fall in pK_a.

Nos. 72—75 represent types of electron-attracting *N*-alkyl substitution which are always base-weakening, as here.

Miscellaneous substituents (Nos. 76—85). The insulating effect of one or two methylene groups is seen in Nos. 76 and 77, where the first proton goes on to the side chain and the first pK_a value approximates to that of benzylamine (9·4) because the interaction between the amino-group and the conjugated system is largely eliminated. There is no colour or fluorescence change on adding the first proton, but addition of the second proton causes a change in colour from cream to yellow and in fluorescence from violet to green, all characteristic of the ionisation of the ring nitrogen in acridine itself and at a similar pK_a. That 5-β-aminoethylacridine can form a di-ion at pH 4 stands in contrast to 5-aminoacridine, which, because of the intense resonance in the mono-ion, gives no (spectrographic) evidence of the formation of a di-ion even in concentrated sulphuric acid (Craig, private communication). It is evident that insulating methylene groups provide a further method for converting weak heterocyclic bases into bases fully ionized at pH 7 without recourse to quaternisation or to ionic resonance.

Nos. 78—82 form a group of acridines with highly conjugated substituents in the 5-position. The fact that certain of these with *p*-amino-substituents (Nos. 78, 80, 82) formed purple to blue mono-ions whilst an isomeride with a *m*-amino-substituent (No. 81) did not, suggested that a base-strengthening resonance might be present, involving both nitrogen atoms. However, the low basic strength shows that this is not the case, and that the separate resonances of the acridine and the phenylene portion of the molecule must be too unrelated for this to occur.

A few partly hydrogenated acridines (Nos. 83—85) are seen not to differ greatly from their acridine analogues, and may be contrasted with the behaviour of pyridine (pK_a 5·0) and its hydrogenation product piperidine (pK_a 11·5).

The effect of acidic substituents is recorded in Table IV. Only derivatives of monoacidic bases (acridine and 2- and 5-aminoacridine) were examined, so that only one of each pair of pK_a values can refer to a cationic ionisation. The correct allocation of the values was simplified by consideration of the ester (Nos. 89, 92, and 97) in which the carbomethoxy-group, as expected, has caused a fall in basic strength (−1·22 to −2·15 pK_a units) intermediate between that shown by the nitro- and the chloro-derivatives. The amide group (in No. 96) behaved similarly.

It is known that the carbomethoxy- and the carboxy-group have an equal effect on the ionisation of another group in the same molecule (Edsall and Blanchard, *J. Amer. Chem. Soc.*, 1933, **55**, 2337). Hence, any differences seen in the present series between the pK_a values of the esters and the corresponding acids must be attributed to the usual interaction between the ionised (acidic and basic) groups of the latter, as in glycine. Such interaction increases the basic strength relative to that of the ester, in the present examples from +1·4 to +1·6 pK_a units (cf. Gane and Ingold, *J.*, 1931, 2153).

The effect of 50% alcohol on the basic constants (as determined in water) provides another diagnostic test for " zwitterion " structure in amino-carboxylic acids, Jukes and Schmidt (*J. Biol. Chem.*, 1934, **105**, 359) having shown that the usual depression of basic strength in bases (see above) is often lacking and a slight elevation may even occur. Although these authors worked only with aliphatic acids, this effect is seen in Nos. 86 and 87. (The pK_a of the acid group is not of diagnostic value, as acid strength is decreased by alcohol whether the compound is a zwitterion or not.)

The three acridine monocarboxylic acids showed only one marked colour change, corresponding to the basic pK_a.

Acridine-1-carboxylic acid and its 5-amino-derivative (Nos. 86 and 94) exhibit an enormous increase in basic strength over their 3-isomerides (ΔpK_a = + 2·56 and +3·7 respectively). This is attributable to Coulombic interaction between the charged groups (Gane and Ingold, *loc. cit.*), which are very close here, and to

TABLE IV.

Ionisation of amphoteric acridines and some derivatives at 20°.

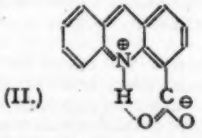
(Determined potentiometrically in 50% ethanol unless otherwise stated. Values marked "H_2O" were determined by absorptiometry in water.)

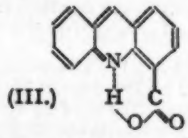
No.	Substance.	Source.	pK_a (basic).	ΔpK_a (basic).	pK_a (acidic).	Dilution.
86	*Acridine-1-carboxylic acid*	M	7·98	+3·87; Acridine	3·1	600
	Acridine-1-carboxylic acid		7·72 (H_2O)	+2·12; Acridine (H_2O)		5,000
87	*Acridine-3-carboxylic acid*	M	5·42	+1·31; Acridine	2·9	1,000
	Acridine-3-carboxylic acid		5·22 (H_2O)	−0·38; Acridine (H_2O)		13,000
88	Acridine-5-carboxylic acid	CC	5·0 (H_2O)	−0·6; Acridine (H_2O)	3	50,000
89	Methyl ester of No. 88	K	3·45 (H_2O)	−2·15; Acridine (H_2O)	None	14,000
90	Acridine-3-sulphonic acid	DD	3·96	−0·15; Acridine	2·5	60
	Acridine-3-sulphonic acid		4·74 (H_2O)	−0·86; Acridine (H_2O)		600
*91	2-Aminoacridine-7-carboxylic acid	EE	8·0 (H_2O)	−0·04; 2-Aminoacridine (H_2O)	2·3	100,000
92	*Methyl* ester of No. 91	M	6·39	−1·22; 2-Aminoacridine	None	300
	Methyl ester of No. 91		7·1 (H_2O)	−0·9; 2-Aminoacridine (H_2O)	None	100,000
*93	2-Aminoacridine-7-sulphonic acid	FF	7·32	−0·29; 2-Aminoacridine		600
	2-Aminoacridine-7-sulphonic acid		7·6 (H_2O)	−0·4; 2-Aminoacridine (H_2O)	<2	21,000
94	5-Aminoacridine-1-carboxylic acid	N	13	+3·6; 5-Aminoacridine	2·7	300
†95	5-Aminoacridine-3-carboxylic acid	N	9·35	−0·1; 5-Aminoacridine	4·06	1,100
96	Amide of No. 95	N	8·20	−1·25; 5-Aminoacridine	None	240
†97	Methyl ester of No. 95	N	7·96	−1·49; 5-Aminoacridine	None	300
*98	5-Amino-1-hydroxyacridine	N	>12	>+2·5; 5-Aminoacridine	7·79	120
	5-Amino-1-hydroxyacridine				7·05 (H_2O)	5,000
*99	5-Amino-2-hydroxyacridine	N	>12	>+2·5; 5-Aminoacridine	7·18	120
	5-Amino-2-hydroxyacridine				6·63 (H_2O)	5,000
*100	5-Amino-3-hydroxyacridine	N	>12	>+2·5; 5-Aminoacridine	8·55	120
	5-Amino-3-hydroxyacridine				7·71 (H_2O)	5,000
*101	5-Amino-4-hydroxyacridine	N	12·3	+2·8; 5-Aminoacridine	6·00	120
	5-Amino-4-hydroxyacridine			+2·8; 5-Aminoacridine	5·61 (H_2O)	5,000

* Some values for these compounds have been previously reported with the basic and acidic pK_a values reversed.
† From these figures the zwitterionic ratio (K_z) in No. 95 is seen to be 7900 (pK_z = 3·90).

K, M, and N; as in Table III.
CC. Homberger and Jensen, *J. Amer. Chem. Soc.*, 1926, **48**, 800.
DD. Matsumura, *ibid.*, 1935, **57**, 1533.
EE. Albert and Goldacre, *J.*, 1943, 454.
FF. Aarons and Albert, *J.*, 1942, 183.

hydrogen bonding which causes the proton to be more firmly attached to the molecule, as in (II), (III) or a resonance hybrid of both. Consequently, the change from $\rangle NH^{\oplus}$ to $\rangle N$ takes place at a higher pH value.





Though zwitterionic nature has not previously been attributed to phenolic derivatives of moderately strong bases (pK_a 8—12), the hydroxy-derivatives of 5-aminoacridine (Nos. 98—100; Table IV) must ionise in this way because the lower pK_a (*e.g.*, 7·71 for 5-amino-3-hydroxyacridine in water) increases when alcohol is added. As this behaviour is not that of a normal basic group, and as the basic group of a zwitterion would have to be the higher of the two values, the lower pK_a is assigned to the acidic group. Further, the bathochromic change at pH 7 on adding alkali (from yellow to orange) is typical of the ionisation of a phenolic group, whereas the hypsochromic change (from orange to yellow) at pH 12 is not.

This increase in acid strength above the values found for the relevant hydroxyacridines (pK_a *ca.* 10) is heightened by resonances involving keto-forms in the 2- and 4-isomerides. Hydrogen bonding between the primary amino-group and the negatively charged oxygen atom (forming a 6-membered ring) still further heightens the acid strength of the 4-isomeride by hindering the approach of hydrogen ions to the oxygen. As there is evidence (see above) for hydrogen bonding in 1-aminoacridine and its derivatives, it is surprising that it is not more discernible in 1-hydroxyacridine (Albert and Goldacre, *loc. cit.*) and 5-amino-1-hydroxyacridine.

In a collateral publication (Albert, Rubbo, Goldacre, Davey, and Stone, *loc. cit.*) these hydroxy-derivatives of 5-aminoacridine were described as anomalous in that they did not exert an antibacterial action proportional to the amount of cation believed to be present (at pH 7·3), the pK_a values being computed by adding 0·5 to the values obtained in 50% alcohol. Direct determination of the pK_a values in water has now revealed the (partly) zwitterionic nature of these compounds, which renders the computation inapplicable. It is now seen that the 3-isomeride (No. 100) contains only 76% cation at pH 7·3 (20°), and the other isomerides still less.

The pK_a values of the two sulphonic acids were assigned by rough analogy to the carboxylic acids although no elevation of the basic pK_a value by alcohol was observed.

Experimental.

Potentiometric Titrations.—These were carried out by running N/20-hydrochloric acid in 50% aqueous alcohol into a mechanically stirred solution of the base (usually 0·00025 g.-mol. in 40 ml.), followed by N/20-potassium hydroxide if acid groups were present. The solution was contained in a thermostatically jacketed beaker containing the glass and the calomel electrode supplied with the Leeds and Northrup Universal pH potentiometer set, to which they were connected with insulated and shielded leads. The set was checked with buffer solutions throughout its pH range. The values obtained were corrected, where necessary, for hydrolysis of the salt formed, and above pH 10, for potassium-ion error. No correction was made for any effect of alcohol on the glass electrode or on the saturated potassium chloride salt junction. Running alkali into a solution of the hydrochloride of a base was avoided, particularly when the base had a high pK_a, to prevent potassium-ion error in the glass electrode. No such error arises with organic cations. A typical result is as follows:

No. 16. 3-*Methylacridine* (50% ethanol; M/60-solution).

% Neutralized	10	21	32	42	53	63	74	84
pK_a	4·61	4·62	4·59	4·58	4·56	4·58	4·62	4·61

With 5-aminoacridine (and with many of its derivatives of pK_a above 9), a slight but definite apparent decline in basic strength is seen after 60% neutralisation and is attributed to association, *e.g.*, one where a resonance association between ion and base causes a proportion of the latter to combine with its own ion. A striking example of this effect is the following:

No. 35. *Benzoflavine* (50% ethanol; M/300-solution).

% Neutralized	27	43	59	75	91
pK_a	9·15	9·14	9·03	8·62	8·2

The tendency to micelle formation of benzoflavine is illustrated by the gelling of a M/50-aqueous solution of its hydrochloride. Gelling does not occur in 50% alcohol, but the titration figures indicate that the micelles are not completely broken up in spite of the lower dielectric constant of the solvent.

Absorptiometry.—A solution of the hydrochloride of the base was added to a series of M/100-buffers of different pH so that the final concentration of the base was about M/10,000. Some substances, notably zwitterions, were so insoluble that they had to be measured at M/50,000. Where precipitation prevented a satisfactory reading being obtained, 50% alcoholic buffers were used. These usually had a pH of about 1 unit higher than the aqueous buffers from which they were prepared (effect of alcohol on the pK_a of the buffer acid). The approximate wave-length of maximum difference in extinction coefficient (ϵ) between the solution of the ion and the base was noted on a Pulfrich photometer, and the extinction measured at intervals of about 0·5 pH unit on a sensitive model Hilger Spekker absorptiometer fitted with Ilford gelatin filters. From the degree of ionisation found at various pH values, the pK_a was calculated and averaged. The difficult determination of the pK_a of 5-aminoacridine, where a suitable difference in ϵ extends over only 40 A., was accomplished by using the 4360 A. mercury line (isolated with a filter).

1-*Amino*-9-*methylacridine.*—3-Methylanthranilic acid, *o*-bromonitrobenzene, and dehydrated potassium carbonate (10 g. of each), catalytic copper (0·1 g.), and *cyclo*hexanol (20 ml.) were refluxed for two hours in a bath at 175°. After steam-distillation, the residual solution was filtered from copper, acidified, and filtered at the boil, giving 12 g. of brown crystals, m. p. 180°. Recrystallisation from 60% alcohol and from 80 parts of benzene gave bright yellow crystals of 2′-*nitro*-6-*methyldiphenylamine*-2-*carboxylic acid*, m. p. 188—189° (Found: C, 62·2; H, 4.4; N, 10·3. $C_{14}H_{12}O_4N_2$ requires C, 61·7; H, 4·45; N, 10·3%). This acid (10 g.) was heated in a boiling water-bath for 15 minutes with sulphuric acid (70 ml.) cautiously poured into boiling water (500 ml.), and the mixture heated for ½ hour on the boiling water-bath. The 1-*nitro*-9-*methylacridone* was filtered off, washed, digested at 80° with dilute ammonia, washed with boiling water, and dried at 120°; yield, 70%, m. p. 226°. After recrystallisation from 50 parts of pyridine trihydrate and then from 150 parts of boiling alcohol, yellow-orange needles, m. p. 228°, were obtained, moderately soluble in glacial acetic acid or toluene (Found: N, 11·0. $C_{14}H_{10}O_3N_2$ requires N, 11·0%). Alcoholic sodium hydroxide gives a scarlet solution of the sodium derivative.

1-Nitro-9-methylacridone (5·3 g.), sodium bicarbonate (26 g.), and alcohol (150 ml. of 90%) were placed in a flask immersed in a bath maintained at 70°, stirred vigorously whilst a rapid stream of carbon dioxide was passed through the suspension, and sodium amalgam (270 g. of 2½%) added during 1½ hours. The contents were then refluxed for an hour, cooled, and filtered. The filtrate was taken to dryness and added to the precipitate, which was then treated with dilute acetic acid until effervescence ceased. The precipitate was freed from mercury and suspended in concentrated hydrochloric acid (50 ml.). Ferric chloride (140 ml. of 10%) was added, and the solution boiled for 15 minutes and filtered. The filtrate was concentrated to 50 ml. and refrigerated, yielding yellow crystals which were powdered, suspended in boiling sodium hydroxide solution, filtered, and recrystallised from light petroleum (50 parts). Yield 50% of 1-*amino*-9-*methylacridine*, yellow-orange needles, m. p. 111°, very soluble in methanol, alcohol, and benzene, all without fluorescence (Found: C, 80·7; H, 5·9; N, 13·4. $C_{14}H_{12}N_2$ requires C, 80·7; 5·9; N, 13·5%). The deep red solution in boiling 0·5N-hydrochloric acid turns pale yellow on cooling and deposits white crystals; this effect is reversible by re-heating. Unlike 1-aminoacridine, it does not give a red colour in 10% acetic acid. The yellow dihydrochloride crystallizes out of concentrated hydrochloric acid on cooling, as happens with 1-aminoacridine. The hydrochlorides do not diazotize normally, but give a white precipitate of the azoimide with nitrous acid, just as 1-aminoacridine does (cf. similar behaviour of 8-aminoquinoline under special conditions, Boehringer, D.R.P., 613,627).

3-*Amino*-5-*methylacridine.* 3-Nitro-5-methylacridine (2·5 g.; Jensen and Rethwisch, *J. Amer. Chem. Soc.*, 1928, **50**, 1144), stannous chloride crystals (11·25 g.), and concentrated hydrochloric acid (15 ml.) were heated in a boiling water-bath for an hour, and treated with sufficient sodium hydroxide solution to redden Orange-II paper. On recrystallisation of the precipitate from alcohol, bright yellow crystals were obtained (80% yield), m. p. 210—211°, unaltered by further recrystallisation (Found: N, 13·3. $C_{14}H_{12}N_2$ requires N, 13·45%). This *substance* was obtained in an impure state by Sharp, Sutherland, and Wilson (*J.*, 1943, 344). The base (1·4 g.) and acetic anhydride (3 ml.) were heated at 105° for ½ hour and washed with light petroleum–benzene (2 : 1). On recrystallisation from alcohol–benzene, pale yellow crystals of 3-acetamido-5-methylacridine, m. p. 273° (sealed tube), were obtained (90% yield) (Found: N, 11·2. Calc. for $C_{16}H_{14}ON_2$: N, 11·2%). The above authors reported m. p. 260° (decomp.), but the late Prof. F. J. Wilson confirmed our sharp m. p. later in 1943, using a sealed tube.

3-*Amino*-5 : 10-*dimethylacridinium bromide* was prepared as 3-amino-10-methylacridinium bromide (Albert and Ritchie, *J.*, 1943, 458) and purified by recrystallisation from 7 parts of water; deep red crystals, remaining hydrated at 110°, m. p. 259—260° (sealed tube) (Found: N, 8·8. $C_{15}H_{15}N_3Br,H_2O$ requires N, 8·7%). The red aqueous solution does not fluoresce. It gives no precipitate with sodium carbonate. Sodium hydroxide gives an immediate pale yellow precipitate of the pseudo-base, soluble in ether, and converted in turn into the red methobromide, and the yellow hydrobromide of the latter, by hydrobromic acid.

3-Aminomethylacridine. 4′-Cyanodiphenylamine-2-carboxylic acid (2·38 g.; Albert and Gledhill, *J. Soc. Chem. Ind.*, 1945, **64**, 169), aqueous ammonia (60 ml. of 10%), and Raney nickel (*ca.* 0·5 g.) were hydrogenated at room temperature and pressure. The mixture was filtered, and the filtrate boiled until free from ammonia, acidified slightly with acetic acid, and refiltered. The precipitate was dried at 120°, extracted with alcohol (30 ml.), taken up in alkali, and the solution stirred with decolorizing carbon, filtered, and acidified with acetic acid, affording *4′-aminomethyldiphenylamine-2-carboxylic acid* (70%) as a yellow-orange solid decomposing at about 200° (sealed tube), practically insoluble in common organic solvents and in water (Found: C, 69·3; H, 6·0; N, 11·5. $C_{14}H_{14}N_2O_2$ requires C, 69·4; H, 5·8; N, 11·6%). The hydrochloride is almost insoluble in water but dissolves readily in alcohol.

The above acid (2 g.) and sulphuric acid (6 ml.) were heated for ½ hour in a boiling water-bath, cooled, poured into water, and made just alkaline to phenolphthalein. The precipitate was dissolved in alcoholic sodium hydroxide, treated with charcoal, filtered, and the *3-aminomethylacridone* precipitated by adding water; bright yellow solid, m. p. 340° (sealed), almost insoluble in all common solvents (Found: C, 74·9; H, 5·5. $C_{14}H_{12}ON_2$ requires C, 75·0; H, 5·4%). It dissolves in concentrated hydrochloric acid and is precipitated on the addition of 2 vols. of water; on further dilution a violet fluorescence appears.

3-Aminomethylacridone (3·4 g.) and alcohol (67 ml.) were stirred for 2 hours at 80° whilst a brisk stream of carbon dioxide was passed through the mixture and sodium amalgam (54 g. of 2½%) added. Stirring and heating were continued for 2 hours more and the mixture was then filtered. The filtrate was taken to dryness, and the residue was dissolved in dilute hydrochloric acid, treated with ferric chloride crystals (8 g.), and boiled for ½ hour. Sodium carbonate was then added to faint alkalinity to litmus, and the solution filtered from iron carbonates. The precipitate was boiled once with water, filtered, and the combined filtrates concentrated to 40 ml. and chilled. The crystals were filtered off, dissolved in water (10 ml.), made faintly alkaline to litmus (precipitate rejected) and then chilled and made alkaline to orange-II paper. The oily precipitate solidified after scratching and refrigeration. It was filtered off and dried in a desiccator. From this crude base (1·6 g.; 50% yield) *3-aminomethylacridine hydrochloride* was prepared by dissolution in water (7 ml.) with 1 equiv. of concentrated hydrochloric acid. After dilution with acetone (7·5 ml.) and refrigeration, the hydrochloride was filtered off, washed with acetone, and dried at 120°, forming a creamy-white powder very soluble in water with violet fluorescence (Found: N, 11·6. $C_{14}H_{12}N_2$,HCl requires N, 11·5%). The dihydrochloride is yellow with a slight orange fluorescence. The free *base* forms buff crystals from 33% methanol and decomposes above 130° without melting sharply. It is volatile in steam and sternutatory. It is soluble in about 5 parts of boiling methanol (with a violet fluorescence) and rather soluble in cold water, but precipitated by excess of sodium hydroxide (Found: C, 80·7; H, 6·0; N, 13·3. $C_{14}H_{12}N_2$ requires C, 80·7; H, 5·8; N, 13·45%). It is decomposed by hot alkaline solutions, and is considerably less stable than 5-aminoethylacridine.

Acridine-1-carboxylic acid. Acridone-1-carboxylic acid (2·75 g.) was stirred with 0·5N-aqueous sodium hydroxide (25 ml.) for 2 hours at 80° whilst sodium amalgam (21 g.; 2½%) was added. The mixture was then boiled for 2 hours, filtered, and the filtrate made acid to methyl-orange with hydrochloric acid. The solution was boiled with a 3-fold excess of ferric chloride, made alkaline with solid sodium carbonate, and filtered whilst hot. The cake was extracted with sodium carbonate solution and the combined filtrates were treated with hydrochloric acid until methyl-orange paper was reddened. The precipitate (2·1 g.) was extracted with alcohol (200 ml.), and the extract concentrated to 15 ml. and diluted with water (60 ml.). *Acridine-1-carboxylic acid* (yield 60%) formed yellow crystals, m. p. 189—190° (Found: C, 75·1; H, 4·1; N, 6·3. $C_{14}H_9O_2N$ requires C, 75·3; H, 4·1; N, 6·3%), moderately soluble in hot water (with gradient) and in alcohol (almost colourless solution with very faint green fluorescence). It is sparingly soluble in benzene, very sparingly soluble in dilute acetic acid, and gives a bright yellow solution in dilute hydrochloric acid with a bright green fluorescence and a pale yellow solution in dilute sodium hydroxide with a moderate green fluorescence.

Acridine-3-carboxylic acid. Acridone-3-carboxylic acid (4 g.) was reduced with aluminium amalgam in water (method of Aarons and Albert, *J.*, 1942, 183). The combined filtrates and washings were treated with ferric chloride at the boil until the green colour of the acridan–acridine meriquinonoid complex disappeared. A great excess of ferric chloride was required because the complex, like the violet complex arising in the reduction of acridone-3-sulphonic acid, is stabilised by the electron-attracting substituent and the usual potassium ferrocyanide test for complete oxidation is invalid.

The precipitate was taken up in sodium carbonate solution, filtered, made neutral to litmus, and the *acridine-3-carboxylic acid* filtered off and recrystallised from aqueous cellosolve, giving buff, sternutatory crystals, decomposing without melting at 270° (Found: C, 75·8; H, 3·9; N, 6·5. $C_{14}H_9O_2N$ requires C, 75·3; H, 4·1; N, 6·3%). It is slightly soluble in water with a green fluorescence that becomes violet on dilution, practically insoluble in all common organic solvents, slightly soluble in dilute hydrochloric acid with a yellow colour and green fluorescence, and very soluble in dilute ammonia with a brilliant blue fluorescence that becomes violet on dilution.

Methyl 2-aminoacridine-7-carboxylate. 2-Aminoacridine-7-carboxylic acid (1 g.; Albert and Goldacre, *J.*, 1943, 454), methanol (10 ml.), and concentrated sulphuric acid (0·6 ml.) were refluxed for 6 hours, poured into ice and water, and made alkaline with sodium carbonate. The precipitate was taken up in cold, dilute acetic acid, the solution filtered, and the filtrate precipitated with sodium carbonate. After recrystallisation from 250 parts of 50% acetone, 0·4 g. of the *methyl* ester was obtained as orange crystals, m. p. 280° (sealed tube) (Found: C, 71·2; H, 4·7; N, 11·2. $C_{15}H_{12}O_2N_2$ requires C, 71·4; H, 4·8; N, 11·1%). It is somewhat soluble in methanol with an orange colour and intense green fluorescence, but almost insoluble in benzene and toluene. The hydrochloride is scarlet and dissolves in water with a green fluorescence. It diazotizes and couples normally.

We wish to thank Prof. J. C. Earl, Dr. I. W. Wark, Dr. H. Hatt, and Mr. K. L. Sutherland for their interest in this work and for helpful discussions; Miss J. Fildes for the microanalyses and Miss M. Sutherland for a gift of styrylacridines. We are grateful to the N.S.W. Department of Agriculture and the Department of Industrial Chemistry of the Council for Scientific & Industrial Research for supplying accommodation and facilities for part of this work during three years. The remainder of the work was supported by the National Health and Medical Research Council and the Wellcome Foundation.

THE UNIVERSITY OF SYDNEY. [*Received, January 29th*, 1946.]

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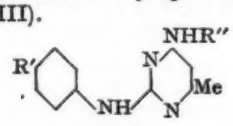
147. *Synthetic Antimalarials. Part VIII. Some 4-Arylamino-6-aminoalkylamino-2-methylpyrimidines.*

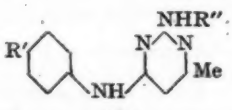
By F. R. BASFORD, F. H. S. CURD, and F. L. ROSE.

In continuation of the work on arylamino-aminoalkylaminopyrimidines described in some of the earlier papers of this series a number of 4-arylamino-6-aminoalkylamino-2-methylpyrimidines of type (III) have been prepared, but were devoid of antimalarial activity. Attention is drawn to a difference between the tautomeric

possibilities in compounds of type (III) on the one hand and the active isomeric 2-arylamino-4-aminoalkylamino- and 4-arylamino-2-aminoalkylamino-6-methylpyrimidines of types (I) and (II) on the other, which may have a bearing on the cause of antimalarial activity. Differences in reactivity between related pyrimidine derivatives are discussed; one possible explanation relates these also to the tautomeric behaviour of the molecules.

In Parts I, II, and VI (this vol., pp. 343, 351, 370) we described the preparation of extensive series of 2-anilino-4-aminoalkylamino-6-methylpyrimidines (I) and 4-anilino-2-aminoalkylamino-6-methylpyrimidines (II) carrying substituents (R′) in the *para* position of the anilino residue. Since compounds of both types (I) and (II) exhibited antimalarial activity against *P. gallinaceum* in chicks it was obviously desirable to examine the third isomeric type (III).


(I.)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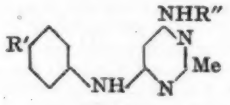
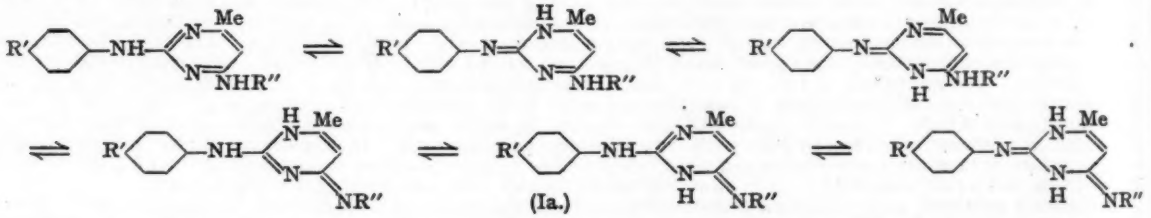
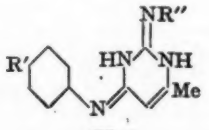
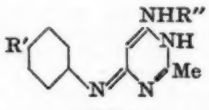

(III.)

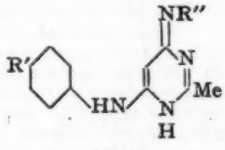
Quite apart from the possibility that the antimalarial activity of compounds of type (I) may be connected with their capability of functioning as riboflavin antagonists, from our initial work (Part I, *loc. cit.*) it appeared to be necessary for the aryl and pyrimidine nuclei to be linked by groupings capable of prototropic change. Compounds of type (II) are similarly constituted, but whereas type (I) conforms to the Schönhöfer hypothesis (*Z. physiol. Chem.*, 1942, **274**, 1), according to which antimalarial activity is associated with an aminoalkylamino group in the γ-position relative to a heterocyclic nitrogen atom so as to allow tautomerism to a *p*-quinonoid structure, type (II) does not. With type (II), only *o*-quinonoid tautomerism is possible, and previously there do not appear to have been any indications that this had any significance for antimalarial activity. It will be seen, however, that types (I) and (II) do possess a common tautomeric feature. The various possibilities in type (I) are as follows:

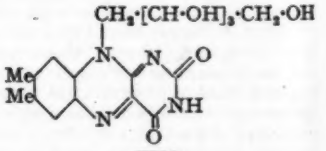

(Ia.)

Similar possibilities exist in type (II), so that in both types the NH-groups linking the phenyl and aminoalkyl residues to the pyrimidine nucleus are simultaneously capable of prototropy as in (Ia) and (IIa). In contrast to this, compounds of type (III), while capable of tautomerism to give the *p*-quinonoid structures (IIIa) and (IIIb), do not permit further prototropic change involving the second heterocyclic nitrogen atom analogous to (Ia) and (IIa). It was therefore considered that an examination of compounds of type (III) might throw further light on the relationship between antimalarial activity and structure.


(IIa.)


(IIIa.)


(IIIb.)

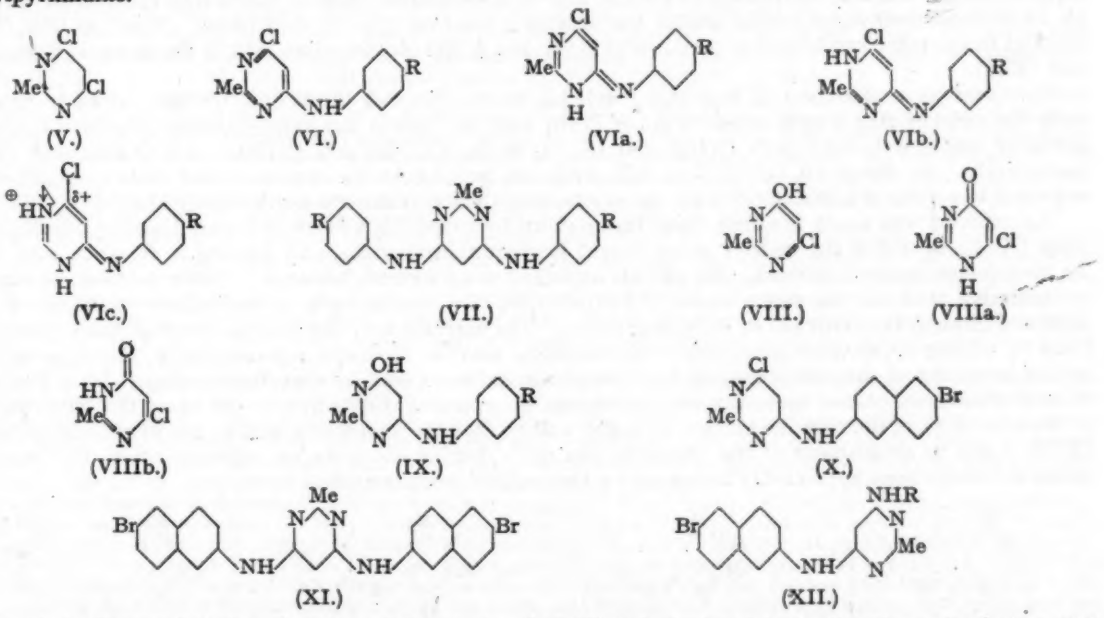

(IV.)

The structural resemblance to riboflavin (IV) discernible in the planar formulations of types (I) and (II) is in certain respects likewise a characteristic of type (III).

Although compounds of types (I) and (II) were not found to be easy of access by the stepwise replacement of the two chlorine atoms in 2 : 4-dichloro-6-methylpyrimidine by arylamino and aminoalkylamino groups respectively, because of the formation of isomeric products which were difficult to separate (see Part VI, this vol., p. 370), such a method had obvious possibilities for the synthesis of compounds of type (III) utilising 4 : 6-dichloro-2-methylpyrimidine (V). In this substance both chlorine atoms are positionally equivalent and the complication of the formation of isomers does not therefore arise. The stepwise replacement of the two chlorine atoms in (V) by amino-groups has been reported by Foldi, von Fodor, Demjén, Szkeres, and Halmos (*Ber.*, 1942, **75**, 755) and by Baddiley, Lythgoe, McNeil, and Todd (*J.*, 1943, 383). Similarly, Huber and Hölscher (*Ber.*, 1938, **71**, 87) found that 4 : 6-dichloro-2 : 5-dimethylpyrimidine required treatment with alcoholic ammonia at a much higher temperature for conversion into 4 : 6-diamino-2 : 5-dimethylpyrimidine than to give 4-chloro-6-amino-2 : 5-dimethylpyrimidine. Further, whereas theory predicts that the two chlorine atoms in 4 : 6-dichloro-2-methylpyrimidine should possess equivalent reactivity, it seemed unlikely that after one had reacted with an arylamine the remaining one would retain its original reactivity, since

new tautomeric possibilities would then have been introduced into the molecule. These considerations led to the hope that condensation of arylamines with (V) could be arrested at the mono-condensation stage.

Exploratory experiments on the condensation of *p*-chloroaniline with (V) to give (VI; R = Cl) showed, however, that this type of reaction proceeded much more readily than the corresponding reaction with ammonia, and in several experiments, even when equimolecular quantities were used, a certain proportion of the dicondensation product (VII; R = Cl) was isolated. The optimum conditions discovered, *viz.*, reaction in acetic acid at 40—50° in presence of a trace of potassium iodide, and in boiling aqueous acetone with the addition of a catalytic amount of hydrochloric acid, yielded products having m. p. 152° and 149—151° respectively. Examination of the latter appeared to indicate that it was not completely pure; the m. p. did not become constant on repeated crystallisation. Although no 4 : 6-*di*-p-*chloroanilino*-2-*methylpyrimidine* (VII; R = Cl) could be separated from this product, an examination of the solubility properties of (VII; R = Cl) (obtained by fusing together at 120° 4 : 6-dichloro-2-methylpyrimidine and two molecular proportions of *p*-chloroaniline with the addition of a little hydrochloric acid) indicated that removal of small quantities from 4-*chloro*-6-p-*chloroanilino*-2-*methylpyrimidine* (VI; R = Cl) would be difficult. Since the use of slightly less than one molecular equivalent of *p*-chloroaniline led to no improvement, it was decided to undertake the synthesis of (VI; R = Cl) by an alternative method in order to assess the purity of the preparations from 4 : 6-dichloro-2-methylpyrimidine.



Dr. P. A. Barrett has shown in these laboratories that (V) is hydrolysed by boiling for a short time with fairly concentrated hydrochloric acid to give 4-*chloro*-6-*hydroxy*-2-*methylpyrimidine* (VIII). On condensation with *p*-chloroaniline this was converted into 4-p-*chloroanilino*-6-*hydroxy*-2-*methylpyrimidine* (IX; R = Cl) which on treatment with boiling phosphoryl chloride yielded 4-chloro-6-*p*-chloroanilino-2-methylpyrimidine, m. p. 152—153°, thus showing that the product previously obtained was only slightly impure, and the reason for the earlier observed variation of the m. p. on repeated crystallisation has not been further investigated.

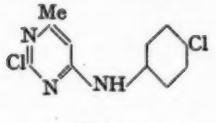
No difference was observed between the 4-*chloro*-6-p-*anisidino*-2-*methylpyrimidine* (VI; R = OMe) obtained by interaction of (V) and *p*-anisidine (1 mol.) in boiling aqueous acetone in presence of a small amount of hydrochloric acid and that from (VIII) *via* 4-p-*anisidino*-6-*hydroxy*-2-*methylpyrimidine* (IX; R = OMe). Interaction of 6-bromo-β-naphthylamine and (V), using equimolecular quantities, gave 4-*chloro*-6-(6′-*bromo*-β-*naphthylamino*)-2-*methylpyrimidine* (X) together with a small proportion of 4 : 6-*di*-(6′-*bromo*-β-*naphthylamino*)-2-*methylpyrimidine* (XI), but separation was easily accomplished in this case because of the insolubility of the dicondensation product in alcohol. The formation of (XI) was entirely prevented by reducing slightly the proportion of amine used. *p*-Nitroaniline reacted with (V) to give 4-*chloro*-6-p-*nitroanilino*-2-*methylpyrimidine* (VI; R = NO_2), either in acetic acid at 50—55° or in boiling aqueous acetone with hydrochloric acid, without any evidence of the formation of dicondensation product.

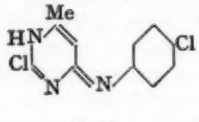
The further reaction of some of these 4-chloro-6-arylamino-2-methylpyrimidines with arylamines was then investigated, boiling aqueous acetone being used as solvent with the addition of small amounts of hydrochloric acid as catalyst. Using these conditions, it had previously been shown that both 2-chloro-4-*p*-chloroanilino-6-methylpyrimidine (XIII) and 4-chloro-2-*p*-chloroanilino-6-methylpyrimidine (XIV) condensed rapidly with a molecule of *p*-chloroaniline to give good yields of 2 : 4-*di*-p-*chloroanilino*-6-*methylpyrimidine* (XV). In contrast to this, no observable reaction had occurred after 2 hours between 4-chloro-6-*p*-chloroanilino-2-methylpyrimidine and *p*-chloroaniline, while 4-chloro-6-anilino-2-methylpyrimidine (VI; R = H)

and aniline, and 4-chloro-6-*p*-anisidino-2-methylpyrimidine (VI; R = OMe) and *p*-anisidine, gave only very small yields of the 4 : 6-diarylamino-compounds. As recorded above it had been observed earlier that the formation of dicondensation product was not easily avoided when 4 : 6-dichloro-2-methylpyrimidine (V) was caused to react with one molecular proportion of *p*-chloroaniline. Employing two molecular proportions of *p*-chloroaniline in aqueous acetone and a trace of hydrochloric acid, the amount of (VII; R = Cl) formed was appreciable. The behaviour of aniline and *p*-anisidine was very similar to that of *p*-chloroaniline except that they appeared to react with greater facility. The former gave approximately equal proportions of the mono- and di-condensation products (VI; R = H) and (VII; R = H), while *p*-anisidine gave almost exclusively (VII; R = OMe) and only a very small proportion of 4-chloro-6-*p*-anisidino-2-methylpyrimidine (VI; R = OMe). Assuming that the reaction proceeds by step-wise replacement of the chlorine atoms, these results suggested that the more difficult second stage, namely the condensation of the intermediate 4-chloro-6-arylamino-2-methylpyrimidine with the second molecule of arylamine, was facilitated by the presence of the equivalent of hydrochloric acid liberated in the first stage. Separate experiments showed this to be so, for when 4-chloro-6-anilino-2-methylpyrimidine and aniline reacted together in aqueous acetone with the addition of slightly more than one equivalent of hydrochloric acid 4 : 6-*dianilino-2-methylpyrimidine* was formed in amount comparable to that obtained from the reaction of (V) with aniline (2 mols.); similarly 4-chloro-6-*p*-chloroanilino-2-methylpyrimidine and *p*-chloroaniline gave a significant amount of 4 : 6-di-*p*-chloroanilino-2-methylpyrimidine within the standard reaction time of two hours. Even so, the chlorine atom in the primary condensation products (VI) was much less reactive than that in the isomeric types (XIII) and (XIV).

One possible explanation of this might well be the tendency of the anilino nitrogen atom to conjugate with the benzene ring giving either (VIa) or (VIb) with the loss of the imino-chloride structure. A similar tendency might well exist with (XIII) and (XIV), giving (XIIIa) and (XIIIb), and (XIVa) and (XIVb), respectively. Of these, all but (XIVa) still retain an imino-chloride structure, and (XIVa) might still be expected to exhibit a labile chlorine by the mechanism (XIVc) (compare 4-chloroquinoline).

An attempt was made to check these speculations by preparing 4-*chloro*-6-N-*methylanilino*-2-*methylpyrimidine* (XVI), in which the methyl group would prevent tautomerism, and causing it to react with aniline by the aqueous acetone method. No (XVII) appeared to be formed, however. This result can be explained by assuming that the resonance forms (XVIa) and (XVIb) predominate, giving effects analogous to those obtained through tautomerism in (VIa) and (VIb). The activation of the chlorine atom in these latter structures by adding appreciable quantities of hydrochloric acid, as observed experimentally, might be explained by the formation of the cation leading to a charge displacement such as that displayed in (VIc). The proton is there arbitrarily placed on a ring nitrogen atom, since such a disposition would exert the optimum effect on the reactivity of the chlorine atom. It might well be that the failure of added hydrochloric acid to activate (XVI) is due to attachment of the proton to the more distant extra-nuclear nitrogen atom, the basicity of which will have been appreciably increased by the methyl group attached to it.


(XIII.)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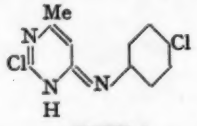
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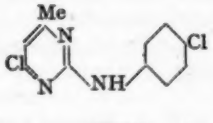
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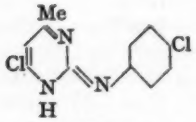
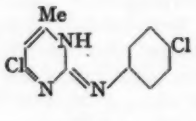

(XIVa.)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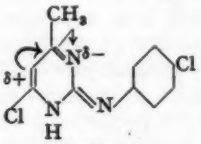
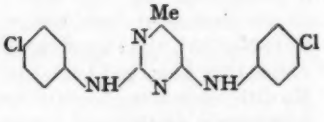
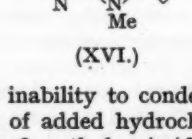

(XIVc.)


(XV.)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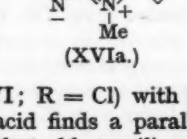
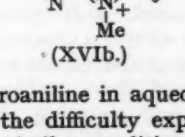

(XVIa.)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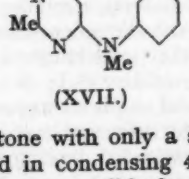
(XVII.)

Our inability to condense (VI; R = Cl) with *p*-chloroaniline in aqueous acetone with only a small proportion of added hydrochloric acid finds a parallel in the difficulty experienced in condensing 4-chloro-6-hydroxy-2-methylpyrimidine with *p*-chloroaniline under similar conditions; this may possibly be connected with a tendency for 4-chloro-6-hydroxy-2-methylpyrimidine to react as (VIIIa) or (VIIIb).

It should be emphasised that none of the condensations discussed above is impossible of achievement since they all proceed to completion at suitably raised temperatures, but the particular conditions used happen to have disclosed the interesting variations in reactivity between the different chloropyrimidines. A further

point of interest in the above experiments is the indication they provide that the nature of the substituent in the anilino group of (VI) affects the reactivity of the chlorine atom and, since we believe this may be bound up with the tautomeric behaviour of the heterocyclic system which also seems important for antimalarial activity, some interesting theoretical arguments can be developed. It is hoped that we shall later have an opportunity of testing these by experiment.

The compounds (VI; R = Cl, OMe, NO_2) and (X) were each condensed with representative aminoalkylamines to give series of substances of types (III) and (XII) which were tested against *P. gallinaceum* in chicks, but none showed any significant activity and in this respect differed from the compounds of types (I) and (II).

Experimental.

4-Chloro-6-hydroxy-2-methylpyrimidine (VIII).—4 : 6-Dichloro-2-methylpyrimidine (Baddiley, Lythgoe, McNeil, and Todd, *loc. cit.*) (25 g.), water (250 c.c.), and hydrochloric acid (100 c.c.) were boiled under reflux for ¾ hour. Complete solution of the chloropyrimidine had occurred after ½ hour. After cooling, the reaction mixture was made alkaline with ammonia and then acidified with acetic acid. After being kept overnight, the precipitated product was filtered off, washed with water, and dried at 100° (yield, 18·4 g.). It crystallised from alcohol in colourless needles, m. p. 233° (Found : N, 19·4; Cl, 24·6. $C_5H_5ON_2Cl$ requires N, 19·4; Cl, 24·6%). *4-Chloro-6-hydroxy-2-methylpyrimidine* is soluble in dilute aqueous ammonia.

4-p-Chloroanilino-6-hydroxy-2-methylpyrimidine (IX; R = Cl).—The above chloropyrimidine (12·2 g.), *p*-chloroaniline (10·6 g.), water (87·5 c.c.), and hydrochloric acid (1·75 c.c.) were boiled under reflux for 6 hours. The reaction mixture was cooled, and the separated product was filtered off, washed with water, and purified by dissolution in warm sodium hydroxide and reprecipitation with acetic acid followed by extraction with dilute ammonia. The undissolved *compound* was crystallised from β-ethoxyethanol, forming small thick colourless prisms, m. p. 296—297° (yield, 7 g.) (Found : C, 55·8; H, 4·1; N, 17·8. $C_{11}H_{10}ON_3Cl$ requires C, 56·05; H, 4·2; N, 17·8%).

4-Chloro-6-p-chloroanilino-2-methylpyrimidine (VI; R = Cl).—(*a*) A mixture of *4-p*-chloroanilino-6-hydroxy-2-methylpyrimidine (5·8 g.) and phosphoryl chloride (30 c.c.) was refluxed for 3 hours. The excess of phosphoryl chloride was removed under reduced pressure and the residue added to ice and water. The solid product was collected and dissolved in alcohol with the addition of sufficient ammonia to give an alkaline reaction, and the solution was filtered and diluted with water. The precipitated *4-chloro-6-p-chloroanilino-2-methylpyrimidine* was collected, washed with water, and crystallised from dilute alcohol; thick colourless prisms, m. p. 152—153° (yield, 3·75 g.) (Found : C, 52·3; H, 3·7; N, 16·6; Cl, 27·7. $C_{11}H_9N_3Cl_2$ requires C, 52·0; H, 3·5; N, 16·5; Cl, 28·0%).

(*b*) 4 : 6-Dichloro-2-methylpyrimidine (4·89 g.) and *p*-chloroaniline (4·4 g.) in glacial acetic acid (30 c.c.) to which a crystal of potassium iodide had been added were stirred at 40—50° for 20 hours. The solution, at first clear, gradually deposited the hydrochloride of the product. After cooling to room temperature anhydrous sodium acetate (3 g.) was added and stirring continued until a clear solution had been obtained. This was then poured into water (250 c.c.), and the precipitated product was collected, washed, and dried. Crystallisation from benzene–light petroleum (b. p. 60—80°) gave (VI; R = Cl), m. p. 152°, undepressed in admixture with material made by method (*a*) above (yield, 7·3 g.) (Found : C, 51·8; H, 3·7; N, 16·2%).

(*c*) 4 : 6-Dichloro-2-methylpyrimidine (8·15 g.), *p*-chloroaniline (6·4 g.), water (40 c.c.), acetone (10 c.c.), and 10N-hydrochloric acid (1 c.c.) were refluxed gently for 1 hour. The solid which had separated was filtered off when cold, suspended in warm alcohol, and ammonia added until alkaline. The resulting solution was diluted with water giving an oil which quickly solidified. The solid was collected and crystallised once from dilute alcohol giving a product (yield, 9·8 g.), m. p. 149—151° undepressed when mixed with 4-chloro-6-*p*-chloroanilino-2-methylpyrimidine made according to method (*a*) (Found : C, 52·3; H, 3·4; N, 16·8; Cl, 26·6, 26·5%).

4-p-Chloroanilino-6-β-diethylaminoethylamino-2-methylpyrimidine (III; R′ = Cl, R″ = $[CH_2]_2$·NEt_2).—4-Chloro-6-*p*-chloroanilino-2-methylpyrimidine (10·16 g.), β-diethylaminoethylamine (11·6 g.), and a crystal of potassium iodide were stirred and heated at 150—160° for 8 hours. The resulting melt was dissolved in warm dilute hydrochloric acid, and the solution was filtered from a small amount of insoluble matter and made alkaline with sodium hydroxide. The precipitated base was extracted with chloroform, the solvent evaporated, and the residue extracted with 5% acetic acid. After being stirred with decolorising carbon, the acetic acid extract was treated with sodium hydroxide and the product again taken into chloroform. Evaporation of the dried chloroform extract left *4-p-chloroanilino-6-β-diethylaminoethylamino-2-methylpyrimidine* which crystallised from light petroleum (b. p. 100—120°) in colourless needles, m. p. 148—149° (yield, 8·4 g.) (Found : C, 61·6; H, 7·2; N, 20·8. $C_{17}H_{24}N_5Cl$ requires C, 61·3; H, 7·2; N, 21·0%) (4079).

4-p-Chloroanilino-6-γ-diethylaminopropylamino-2-methylpyrimidine (III; R′ = Cl, R″ = $[CH_2]_3$·NEt_2).—4-Chloro-6-*p*-chloroanilino-2-methylpyrimidine (8·45 g.) and γ-diethylaminopropylamine (5·37 g.) were heated at 140—150° for 8 hours with stirring and the reaction mixture worked up as described above, giving a *product* which crystallised from light petroleum (b. p. 100—120°) as colourless prisms, m. p. 128° (Found : C, 61·8; H, 7·2; N, 20·0. $C_{18}H_{26}N_5Cl$ requires C, 62·2; H, 7·5; N, 20·1%) (3597).

The following were prepared in a similar way.

4-p-Chloroanilino-6-γ-di-n-butylaminopropylamino-2-methylpyrimidine (III; R′ = Cl, R″ = $[CH_2]_3$·NBu_2), from 4-chloro-6-*p*-chloroanilino-2-methylpyrimidine (2·54 g.) and γ-di-*n*-butylaminopropylamine (3·72 g.), crystallised from light petroleum (b. p. 60—80°) in colourless needles, m. p. 93—94° (Found : C, 65·1; H, 8·1; N, 17·3; Cl, 8·9. $C_{22}H_{34}N_5Cl$ requires C, 65·4; H, 8·4; N, 17·4; Cl, 8·7%) (4562).

4-p-Chloroanilino-6-γ-piperidinopropylamino-2-methylpyrimidine (III; R′ = Cl, R″ = $[CH_2]_3$·N<$[CH_2]_4$>CH_2), from 4-chloro-6-*p*-chloroanilino-2-methylpyrimidine (7·65 g.) and γ-piperidinopropylamine (5·3 g.), crystallised from light petroleum (b. p. 100—120°) in flat colourless prisms, m. p. 110° (Found : C, 62·9; H, 6·9; N, 19·3; Cl, 10·1. $C_{19}H_{26}N_5Cl$ requires C, 63·4; H, 7·2; N, 19·5; Cl, 10·0%) (5273).

4-p-Chloroanilino-6-δ-diethylamino-α-methylbutylamino-2-methylpyrimidine (III; R′ = Cl, R″ = CHMe·$[CH_2]_3$·NEt_2) (3720), from 4-chloro-6-*p*-chloroanilino-2-methylpyrimidine and δ-diethylamino-α-methylbutylamine, formed a practically colourless oil, b. p. 222—224°/0·1 mm. (Found : Cl, 9·4. $C_{20}H_{30}N_5Cl$ requires Cl, 9·4%). It gave a *dipicrate* which separated from β-ethoxyethanol in microscopic yellow plates, m. p. 149—151° (Found : C, 46·3; H, 4·4; N, 18·4. $C_{20}H_{30}N_5Cl,2C_6H_3O_7N_3$ requires C, 46·1; H, 4·3; N, 18·5%). The dihydrochloride was hygroscopic and could not be satisfactorily crystallised.

4-p-Chloroanilino-6-γ-(β′-diethylaminoethoxy)propylamino-2-methylpyrimidine (III; R′ = Cl, R″ = $[CH_2]_3$·O·$[CH_2]_2$·NEt_2), from 4-chloro-6-*p*-chloroanilino-2-methylpyrimidine and γ-(β′-diethylaminoethoxy)propylamine, formed a colourless oil, b. p. 245—249°/0·15 mm. (Found : N, 17·9. $C_{20}H_{30}ON_5Cl$ requires N, 17·9%). The *dipicrate* separated from β-ethoxyethanol as a yellow microcrystalline powder, m. p. 181—182° (Found : C, 45·0; H, 4·2; N, 18·0. $C_{20}H_{30}ON_5Cl,2C_6H_3O_7N_3$ requires C, 45·2; H, 4·2; N, 18·1%).

4-p-*Anisidino*-6-*hydroxy*-2-*methylpyrimidine* (IX; R = OMe).—4-Chloro-6-hydroxy-2-methylpyrimidine (8·0 g.) and *p*-anisidine (6·15 g.) were mixed, hydrochloric acid (0·5 c.c.) was added, and the mixture heated at 120—130° for 3 hours, with stirring until the melt solidified. The resulting solid mass was ground, dissolved in warm dilute sodium hydroxide, treated with decolorising carbon, and filtered. Addition of acetic acid to the filtrate precipitated the *product* which was purified by stirring with dilute ammonia followed by crystallisation from β-ethoxyethanol; colourless laminæ, m. p. 266—268° (Found: C, 62·3; H, 5·3; N, 18·9. $C_{12}H_{13}O_2N_3$ requires C, 62·3; H, 5·6; N, 18·2%) (yield, 8 g.).

4-*Chloro*-6-p-*anisidino*-2-*methylpyrimidine* (VI; R = OMe).—(*a*) The above hydroxy compound (6 g.) and phosphoryl chloride (30 c.c.) were refluxed during 1·5 hours. The resulting mixture was poured on ice and made alkaline with ammonia. The solid obtained was filtered off, dissolved in alcohol with the addition of a little ammonia, and poured into water. The product reprecipitated in this way crystallised from dilute alcohol giving 4-*chloro*-6-p-*anisidino*-2-*methylpyrimidine* as thick colourless laminæ, m. p. 142—143° (Found: C, 57·9; H, 4·7; N, 16·6; Cl, 14·1. $C_{12}H_{12}ON_3Cl$ requires C, 57·7; H, 4·8; N, 16·8; Cl, 14·2%) (yield, 3·7 g.).

(*b*) 4 : 6-Dichloro-2-methylpyrimidine (16·3 g.), *p*-anisidine (12·3 g.), water (80 c.c.), acetone (20 c.c.), and 10N-hydrochloric acid (2 c.c.) were boiled for 1 hour and the resulting solution cooled. The crystalline product which separated was collected, suspended in warm alcohol, and ammonia added until alkaline. When solution had occurred, water was added and the precipitated product was filtered off, washed with water, and purified by crystallisation from aqueous methanol giving material identical with (*a*) above, m. p. and mixed m. p. 141—143° (yield, 15·2 g.) (Found: C, 57·4; H, 4·9; N, 16·5; Cl, 13·7%).

4-p-*Anisidino*-6-β-*diethylaminoethylamino*-2-*methylpyrimidine* (III; R′ = OMe; R″ = $[CH_2]_2$·NEt_2).—A mixture of the above chloropyrimidine (2·5 g.) and β-diethylaminoethylamine (2·5 g.) to which a crystal of potassium iodide had been added was heated at 150—160° for 8 hours. The whole was then dissolved in dilute hydrochloric acid and the solution made alkaline with sodium hydroxide. The precipitated product was filtered off and dissolved in 5% acetic acid, and the solution was treated with decolorising carbon and filtered. Addition of sodium hydroxide to the filtrate gave a solid which was collected, washed with water, and dried. Crystallised from light petroleum (b. p. 100—120°) the *compound* was obtained as colourless prisms, m. p. 146—148° (Found: C, 65·7; H, 7·7; N, 21·4. $C_{18}H_{27}ON_5$ requires C, 65·7; H, 8·2; N, 21·3%) (4071).

4-p-*Anisidino*-6-γ-*diethylaminopropylamino*-2-*methylpyrimidine* (III; R′ = OMe, R″ = $[CH_2]_3$·NEt_2), obtained in a similar manner by using γ-diethylaminopropylamine in place of β-diethylaminoethylamine, formed flat colourless prisms from light petroleum (b. p. 100—120°), m. p. 130° (Found: C, 66·0; H, 8·3; N, 20·0. $C_{19}H_{29}ON_5$ requires C, 66·5; H, 8·5; N, 20·4%) (3610).

4-p-*Anisidino*-6-δ-*diethylamino*-α-*methylbutylamino*-2-*methylpyrimidine* (III; R′ = OMe, R″ = CHMe·$[CH_2]_3$·NEt_2).—4-Chloro-6-*p*-anisidino-2-methylpyrimidine (5·0 g.) and δ-diethylamino-α-methylbutylamine (4·8 g.) were mixed and fused at 150—160° for 7 hours. The cooled melt was dissolved in dilute hydrochloric acid and the solution made alkaline with sodium hydroxide and extracted with chloroform. The solvent was evaporated and the residue stirred with 5% acetic acid. The acid extract was clarified with decolorising carbon and then treated with sodium hydroxide. The liberated base was taken up in chloroform, and the chloroform solution was dried and evaporated. The *product* remained as an oil which crystallised on stirring with light petroleum (b. p. 40—60°). It was collected and purified by crystallisation from light petroleum (b. p. 60—80°); colourless prisms, m. p. 103° (Found: C, 68·0; H, 8·9; N, 19·2. $C_{21}H_{33}ON_5$ requires C, 67·9; H, 8·9; N, 18·9%) (3679).

4-*Chloro*-6-p-*nitroanilino*-2-*methylpyrimidine* (VI; R = NO_2).—(*a*) 4 : 6-Dichloro-2-methylpyrimidine (4·89 g.), *p*-nitroaniline (4·55 g.), glacial acetic acid (50 c.c.), and a crystal of potassium iodide were heated at 50—55° for 18 hours. Addition of sodium acetate (3 g.) and dilution with water (250 c.c.) gave 4-*chloro*-6-p-*nitroanilino*-2-*methylpyrimidine* which crystallised from butanol in yellow needles, m. p. 271—272° (Found: Cl, 13·5. $C_{11}H_9O_2N_4Cl$ requires Cl, 13·4%).

(*b*) 4 : 6-Dichloro-2-methylpyrimidine (16·3 g.), *p*-nitroaniline (13·8 g.), water (75 c.c.), acetone (25 c.c.), and 10N-hydrochloric acid (2 c.c.) were refluxed for 2 hours. After cooling, the product which had separated was filtered off and dried. It was then dissolved in hot β-ethoxyethanol with the addition of ammonia to make the solution alkaline to Brilliant Yellow, and the solution was diluted with a large volume of water. The precipitated chloropyrimidine was filtered off, washed with water, and dried. Crystallisation from β-ethoxyethanol gave the same product as (*a*), m. p. 271—272° (Found: C, 50·3; H, 3·6; N, 20·7. $C_{11}H_9O_2N_4Cl$ requires C, 49·9; H, 3·4; N, 21·2%).

4-p-*Nitroanilino*-6-β-*diethylaminoethylamino*-2-*methylpyrimidine* (III; R′ = NO_2; R″ = $[CH_2]_2$·NEt_2).—4-Chloro-6-*p*-nitroanilino-2-methylpyrimidine (5·28 g.) and β-diethylaminoethylamine (4·6 g.) condensed together by heating at 150—160° for 6 hours and worked up in the usual way for this type of compound gave the *base* which crystallised from benzene in yellow prisms, m. p. 130—131° (Found: C, 59·2; H, 6·8; N, 24·4. $C_{17}H_{24}O_2N_6$ requires C, 59·3; H, 7·0; N, 24·4%) (4148).

4-p-*Nitroanilino*-6-γ-*dimethylaminopropylamino*-2-*methylpyrimidine* (III; R′ = NO_2, R″ = $[CH_2]_3$·NMe_2), from the same chloropyrimidine and γ-dimethylaminopropylamine, separated from toluene in small yellow needles, m. p. 169° (Found: C, 58·3; H, 6·9; N, 25·2. $C_{16}H_{22}O_2N_6$ requires C, 58·2; H, 6·7; N, 25·45%) (4189).

4-p-*Nitroanilino*-6-γ-*di*-n-*butylaminopropylamino*-2-*methylpyrimidine* (III; R′ = NO_2, R″ = $[CH_2]_3$·NBu_2), prepared likewise using γ-di-*n*-butylaminopropylamine, crystallised from light petroleum (b. p. 80—100°) in small yellow needles, m. p. 101° (Found: C, 63·6; H, 8·5; N, 20·3. $C_{22}H_{34}O_2N_6$ requires C, 63·8; H, 8·2; N, 20·3%) (4563).

4-*Chloro*-6-(6′-*bromo*-β-*naphthylamino*)-2-*methylpyrimidine* (X).—(*a*) 4 : 6-Dichloro-2-methylpyrimidine (8·15 g.) and 6-bromo-β-naphthylamine (11·1 g.) were ground together, acetic acid (3 g.) was added, and the mixture heated to 120°; a vigorous reaction set in and the whole solidified. After being heated at 110—120° for 15 minutes the product was ground and stirred with water (100 c.c.) and ammonia (10 c.c.) for several hours. The resulting solid was filtered off, washed with water, and dried. It was then boiled with alcohol (250 c.c.) and a few drops of ammonia for ½ hour and filtered hot, leaving an insoluble residue which was retained. The alcoholic filtrate was evaporated to dryness, the residue stirred with water, and the resulting solid dried. Crystallisation from toluene gave 4-*chloro*-6-(6′-*bromo*-β-*naphthylamino*)-2-*methylpyrimidine* as thick colourless prisms, m. p. 191—192° (Found: C, 52·1; H, 3·4; N, 12·05. $C_{15}H_{11}N_3ClBr$ requires C, 51·7; H, 3·2; N, 12·05%) (yield, 9 g.). The above residue, insoluble in alcohol, crystallised from glacial acetic acid in colourless hair-fine needles, m. p. 284—285° (Found: C, 56·2; H, 4·0; N, 10·6; Br, 30·0. $C_{25}H_{18}N_4Br_2$ requires C, 56·2; H, 3·4; N, 10·6; Br, 30·0%), and consisted of 4 : 6-*di*-(6′-*bromo*-β-*naphthylamino*)-2-*methylpyrimidine* (yield, 3·3 g.).

(*b*) 4 : 6-Dichloro-2-methylpyrimidine (8·15 g.), 6-bromo-β-naphthylamine (10·5 g.), water (60 c.c.), acetone (40 c.c.), and 10N-hydrochloric acid (1 c.c.) were refluxed gently for 1½ hours. During the course of the reaction a solid separated. This was filtered off, after cooling, and washed with water. It was then dissolved in hot alcohol with the addition of ammonia to give an alkaline reaction and the solution poured into water. The precipitated product was filtered off, washed with water, dried, and crystallised from toluene giving 4-chloro-6-(6′-bromo-β-naphthylamino)-2-methylpyrimidine, m. p. 191—192°, identical with that made by method (*a*) (yield, 10·45 g.) (Found: C, 52·0; H, 3·3; N, 12·3%).

When the amount of 6-bromo-β-naphthylamine used in the above experiment was increased to 11·1 g. (1 mol.)

there were obtained 4-chloro-6-(6′-bromo-β-naphthylamino)-2-methylpyrimidine (9·05 g.) and 4 : 6-di-(6′-bromo-β-naphthyl amino)-2-methylpyrimidine (1·8 g.).

4-(6′-Bromo-β-naphthylamino)-6-β-diethylaminoethylamino-2-methylpyrimidine (XII; R = $[CH_2]_2$·NEt_2).—4-Chloro-6-(6′-bromo-β-naphthylamino)-2-methylpyrimidine (4·5 g.) was heated with β-diethylaminoethylamine (3·6 g.) at 150—160° for 6 hours. A solution of the resulting product in dilute hydrochloric acid was made alkaline with sodium hydroxide and the precipitated oil taken into chloroform. After removal of the chloroform the residue was extracted with 5% acetic acid, the extract treated with sodium hydroxide, and the liberated product extracted with chloroform. Evaporation of the dried chloroform solution and crystallisation of the residue from light petroleum (b. p. 100—120°) afforded *4-(6′-bromo-β-naphthylamino)-6-β-diethylaminoethylamino-2-methylpyrimidine*; clumps of colourless prisms, m. p. 129—131° (Found : 59·1; H, 6·6; N, 16·2. $C_{21}H_{26}N_5Br$ requires C, 58·7; H, 6·1; N, 16·4%) (3960).

The following were prepared in a similar way.

4-(6′-Bromo-β-naphthylamino)-6-γ-diethylaminopropylamino-2-methylpyrimidine (XII; R = $[CH_2]_3$·NEt_2), from (X) and γ-diethylaminopropylamine, crystallised from light petroleum (b. p. 100—120°) in flat colourless prisms, m. p. 129—130° (Found : C, 59·7; H, 6·7; N, 15·7; Br, 18·1. $C_{22}H_{28}N_5Br$ requires C, 59·7; H, 6·3; N, 15·8; Br, 18·1%) (3948).

4-(6′-Bromo-β-naphthylamino)-6-γ-dimethylaminopropylamino-2-methylpyrimidine (XII; R = $[CH_2]_3$·NMe_2), from (X) and γ-dimethylaminopropylamine, crystallised from light petroleum (b. p. 100—120°); m. p. 132—134° (Found : C, 57·9; H, 5·6; N, 16·5. $C_{20}H_{24}N_5Br$ requires C, 58·0; H, 5·8; N, 16·9%) (3989).

4-(6′-Bromo-β-naphthylamino)-6-γ-di-n-*butylaminopropylamino-2-methylpyrimidine* (XII; R = $[CH_2]_3$·NBu_2), from (X) and γ-di-*n*-butylaminopropylamine, crystallised from light petroleum (b. p. 60—80°) in colourless prisms, m. p. 91—93° (Found : C, 62·5; H, 6·7; N, 14·1. $C_{28}H_{34}N_5Br$ requires C, 62·7; H, 7·2; N, 14·1%) (4564).

4-(6′-Bromo-β-naphthylamino)-6-δ-diethylamino-α-methylbutylamino-2-methylpyrimidine (XIII; R=CHMe·$[CH_2]_3$·NEt_2), from (X) and δ-diethylamino-α-methylbutylamine, crystallised from light petroleum (b. p. 60—80°) in clumps of colourless prisms, m. p. 109—110° (Found : C, 61·3; H, 6·8; N, 15·1. $C_{24}H_{32}N_5Br$ requires C, 61·3; H, 6·8; N, 14·9%) (3961).

2 : 4-*Di*-p-*chloroanilino*-6-*methylpyrimidine* (XV).—(*a*) 2 : 4-Dichloro-6-methylpyrimidine (10 g.) and *p*-chloroaniline (34 g.) were heated in boiling β-ethoxyethanol (100 c.c.) for 2½ hours. The reaction mixture was then poured into water, made alkaline with ammonia, and steam distilled to remove unchanged *p*-chloroaniline. The solid *product* was filtered off, washed with water, and dried. Crystallisation from alcohol gave fine colourless needles, m. p. 167—168° (Found : C, 59·0; H, 4·05; N, 16·1; Cl, 20·7. $C_{17}H_{14}N_4Cl_2$ requires C, 59·1; H, 4·05; N, 16·2; Cl, 20·6%).

(*b*) 2-Chloro-4-*p*-chloroanilino-6-methylpryimidine (Curd *et al.*, this vol., p. 373) (5·1 g.), *p*-chloroaniline (2·55 g.), water (30 c.c.), acetone (15 c.c.), and 10N-hydrochloric acid (0·5 c.c.) were refluxed for 2 hours. The product began to separate after a few minutes. The filtered (cold) product was dissolved in hot alcohol with the addition of ammonia and then precipitated with water, collected, and dried. Crystallisation from ethyl acetate–light petroleum gave 2 : 4-di-*p*-chloroanilino-6-methylpyrimidine (6·1 g.), m. p. and mixed m. p. 167—168°.

(*c*) 4-Chloro-2-*p*-chloroanilino-6-methylpyrimidine (Part I, this vol., p. 349) (5·1 g.) and *p*-chloroaniline (2·55 g.) condensed together under the same conditions to give 2 : 4-di-*p*-chloroanilino-6-methylpyrimidine (6·2 g.), m. p. and mixed m. p. 167—168°.

4 : 6-*Di*-p-*chloroanilino*-2-*methylpyrimidine* (VII; R = Cl).—(*a*) 4 : 6-Dichloro-2-methylpyrimidine (3·2 g.) and *p*-chloroaniline (5·0 g.) were mixed, hydrochloric acid (5 drops) was added, and the mixture heated at 120° for 2 hours. Water was then added and the product collected. It was then suspended in hot alcohol and dissolved by the addition of ammonia. Addition of water precipitated 4 : 6-*di*-p-*chloroanilino*-2-*methylpyrimidine* which crystallised from alcohol in colourless prisms, m. p. 216—218° (Found : C, 59·6; H, 4·1; N, 16·3; Cl, 20·6. $C_{17}H_{14}N_4Cl_2$ requires C, 59·1; H, 4·1; N, 16·2; Cl, 20·6%).

(*b*) 4 : 6-Dichloro-2-methylpyrimidine (4·1 g.), *p*-chloroaniline (6·4 g.), water (20 c.c.), acetone (5 c.c.), and 10N-hydrochloric acid (0·5 c.c.) were refluxed for 2 hours. After cooling, the product which had separated was filtered off, dissolved in alcohol, and made alkaline with ammonia. Dilution with water precipitated a solid which was collected, dried, and crystallised from alcohol giving 4 : 6-di-*p*-chloroanilino-2-methylpyrimidine (2·4 g.), m. p. 215—217°, unaltered when mixed with material from (*a*). Dilution of the mother liquor with water precipitated 4-chloro-6-*p*-chloroanilino-2-methylpyrimidine (3·55 g.), m. p. 146—148°.

Condensation of 4-*Chloro*-6-p-*chloroanilino*-2-*methylpyrimidine with* p-*Chloroaniline*.—4-Chloro-6-*p*-chloroanilino-2-methylpyrimidine (5·1 g.), *p*-chloroaniline (2·55 g.), water (30 c.c.), acetone (20 c.c.), and 10N-hydrochloric acid (2·25 c.c.) were boiled under reflux for 2 hours and then cooled. The filtered product was dissolved in alcohol with the addition of ammonia and then precipitated with water. By fractional crystallisation from alcohol it was separated into 4 : 6-di-*p*-chloroanilino-2-methylpyrimidine (1 g.), m. p. and mixed m. p. 216—217°, and unchanged starting material (3·6 g.). When the amount of 10N-hydrochloric acid in the above experiment was reduced to 0·5 c.c. only unchanged starting material could be isolated.

4-Anilino-6-hydroxy-2-methylpyrimidine (IX; R = H).—4-Chloro-6-hydroxy-2-methylpyrimidine (21·67 g.), aniline (13·95 g.), and hydrochloric acid (1 c.c.) were mixed and heated to 150—160°. A vigorous reaction ensued and the reaction mixture set solid. After being heated at the above temperature for 1 hour the cooled and ground melt was dissolved in dilute sodium hydroxide solution, treated with decolorising carbon, and filtered. The filtrate was acidified with acetic acid and the precipitated product filtered off. Purification from any unchanged 4-chloro-6-hydroxy-2-methylpyrimidine was then effected by stirring with dilute ammonia, and the product was again collected, washed with water, and dried. By crystallisation from β-ethoxyethanol the *compound* was obtained as thick colourless laminæ, m. p. 276° (Found : C, 65·1; H, 5·5; N, 20·7. $C_{11}H_{11}ON_3$ requires C, 65·7; H, 5·5; N, 20·9%).

4-Chloro-6-anilino-2-methylpyrimidine (VI; R = H).—The above hydroxypyrimidine (20 g.) and phosphoryl chloride (100 c.c.) were refluxed for 9 hours and the resulting mixture worked up as described for the preparation of the corresponding *p*-chloroanilino compound [method (*a*)] giving the *chloropyrimidine* as colourless prisms from light petroleum (b. p. 100—120°), m. p. 134—135° (Found : C, 60·0; H, 4·6; N, 19·6; Cl, 16·2. $C_{11}H_{10}N_3Cl$ requires C, 60·1; H, 4·6; N, 19·1; Cl, 16·2%).

Condensation of 4 : 6-*Dichloro*-2-*methylpyrimidine with Aniline*.—4 : 6-Dichloro-2-methylpyrimidine (4·1 g.) and aniline (4·6 g.) were added to a mixture of water (20 c.c.) and acetone (5 c.c.) to which 10N-hydrochloric (0·5 c.c.) had been added, and the mixture was refluxed for 2 hours. After cooling, the clear solution was poured into dilute ammonia and the precipitated solid filtered off. To ensure complete basification the product was dissolved in a hot mixture of β-ethoxyethanol and alcohol, ammonia added to alkalinity, and the solution poured into water. Crystallisation of the dried precipitated product from *n*-propanol gave 4 : 6-*dianilino*-2-*methylpyrimidine* (3·1 g.) as flat colourless prisms, m. p. 242—243° (Found : C, 73·8; H, 5·6; N, 20·5. $C_{17}H_{16}N_4$ requires C, 73·9; H, 5·8; N, 20·3%). Dilution of the *n*-propanol mother liquors with water gave 4-chloro-6-anilino-2-methylpyrimidine (2 g.), m. p. and mixed m. p. 134—135°.

Condensation of 4-*Chloro*-6-*anilino*-2-*methylpyrimidine with Aniline*.—4-Chloro-6-anilino-2-methylpyrimidine (5·49 g.),

aniline (2·32 g.), water (40 c.c.), acetone (10 c.c.), and 10N-hydrochloric acid (0·5 c.c.) were heated under reflux for 2 hours. After dilution of the resulting reaction mixture with water and addition of ammonia the product was collected by filtration. It was then dissolved in hot β-ethoxyethanol, and the solution was made alkaline with ammonia and poured into water. The solid thus precipitated was collected, dried, and dissolved in the minimum quantity of hot alcohol. On cooling, 4 : 6-dianilino-2-methylpyrimidine (0·85 g.), m. p. and mixed m. p. 241—242°, separated. Dilution of the mother liquors with water yielded only unchanged starting material (3·6 g.), m. p. and mixed m. p. 135°.

Repetition of the above experiment using an increased amount of 10N-hydrochloric acid (3 c.c.) gave 4 : 6-dianilino-2-methylpyrimidine (2·8 g.) and unchanged 4-chloro-6-anilino-2-methylpyrimidine (2·4 g.).

Condensation of 4 : 6-*Dichloro-2-methylpyrimidine with* p-*Anisidine.*—4 : 6-Dichloro-2-methylpyrimidine (4·1 g.), *p*-anisidine (6·2 g.), water (20 c.c.), acetone (5 c.c.), and 10N-hydrochloric acid (0·5 c.c.) were refluxed for 2 hours. After cooling, the product which had separated was filtered off and dissolved in alcohol, and the solution, after being made alkaline with ammonia, was poured into water. The precipitated solid was filtered off, washed, and dried. Crystallisation from β-ethoxyethanol gave 4 : 6-*di*-p-*anisidino-2-methylpyrimidine* as colourless laminæ, m. p. 211—212° (Found: C, 67·9; H, 6·2; N, 17·3. $C_{19}H_{20}O_2N_4$ requires C, 67·9; H, 6·0; N, 16·7%) (yield, 4 g.). Dilution of the mother liquors with water gave 4-chloro-6-*p*-anisidino-2-methylpyrimidine (1 g.), m. p. and mixed m. p. 142—144°.

Condensation of 4-*Chloro*-6-p-*anisidino-2-methylpyrimidine with* p-*Anisidine.*—4-Chloro-6-*p*-anisidino-2-methylpyrimidine (3·3 g.) and *p*-anisidine (1·63 g.) were boiled with water (20 c.c.) and acetone (5 c.c.), to which 10N-hydrochloric acid (0·25 c.c.) had been added, during 2 hours. When worked up in the same way as in the previous experiment a crude product was obtained which on boiling with alcohol was separated into the insoluble 4 : 6-di-*p*-anisidino-2-methylpyrimidine (0·9 g.), m. p. 211°, and soluble 4-chloro-6-*p*-anisidino-2-methylpyrimidine (1·8 g.), m. p. 142°.

4-N-*Methylanilino-6-hydroxy-2-methylpyrimidine.*—This was prepared by condensation of 4-chloro-6-hydroxy-2-methylpyrimidine (14·45 g.) and methylaniline (10·7 g.), with the addition of hydrochloric acid (0·75 c.c.), at 150—160°, followed by working up as described for the corresponding anilino compound. The *base* separated from β-ethoxyethanol in thick colourless prisms, m. p. 263° (Found: C, 67·2; H, 6·4; N, 19·3. $C_{12}H_{13}ON_3$ requires C, 67·0; H, 6·0; N, 19·5%).

4-*Chloro*-6-N-*methylanilino-2-methylpyrimidine.*—(*a*) Treatment of the preceding hydroxypyrimidine (15 g.) with boiling phosphoryl chloride (75 c.c.) during 2 hours followed by working up in the manner described above for similar preparations gave the *chloro*-compound, which crystallised from aqueous methanol in flat colourless prisms, m. p. 74—75° (Found: C, 61·6; H, 5·15; Cl, 15·5. $C_{12}H_{12}N_3Cl$ requires C, 61·7; H, 5·1; Cl, 15·2%).

(*b*) 4 : 6-Dichloro-2-methylpyrimidine (8·2 g.) and methylaniline (5·35 g.) were added to a mixture of water (40 c.c.), acetone (10 c.c.), and 10N-hydrochloric acid (1 c.c.), and the whole was boiled under reflux for 6 hours. After dilution with water and addition of ammonia to give an alkaline reaction the product was filtered off. To ensure complete conversion of the hydrochloride into the base, the product was dissolved in alcohol, sufficient ammonia added to give an alkaline reaction, and the solution poured into excess of water. The precipitated product was then collected and crystallised from dilute methanol; m. p. 74—75° undepressed in admixture with material made by method (*a*).

4-*Anilino*-6-N-*methylanilino-2-methylpyrimidine.*—4-Chloro-6-anilino-2-methylpyrimidine (5·49 g.) and methylaniline (2·68 g.) were mixed, 10N-hydrochloric acid (0·5 c.c.) was added, and the mixture heated at 130—140° for 3 hours. The resulting melt (solid) was cooled, ground, and dissolved in boiling β-ethoxyethanol. The solution was then made distinctly alkaline by addition of ammonia and poured into excess of water. The precipitated *base* was filtered off, dried, and crystallised from *n*-propanol; thick colourless needles, m. p. 150° (Found: C, 74·1; H, 6·1. $C_{18}H_{18}N_4$ requires C, 74·5; H, 6·2%).

An attempt was made to prepare this compound by condensation of 4-chloro-6-*N*-methylanilino-2-methylpyrimidine (5·84 g.) and aniline (2·32 g.) in a mixture of water (40 c.c.) and acetone (10 c.c.) in presence of 10-N-hydrochloric acid (0·5 c.c.) by boiling for 2 hours. No detectable condensation occurred and only unchanged compound could be isolated. Increasing the amount of hydrochloric acid to 3 c.c. had no effect.

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148. *Synthetic Antimalarials. Part IX. 4-Arylamino-2-aminoalkylamino-6-methylpyrimidines. Further Variations.*

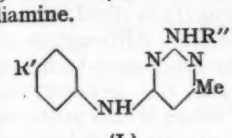
By F. H. S. CURD, (MISS) M. I. DAVIS, E. C. OWEN, F. L. ROSE, and G. A. P. TUEY.

Curd, Davis, Owen, Rose, and Tuey (Part VI, this vol., p. 370) described a series of 4-arylamino-2-aminoalkylamino-6-methylpyrimidines some of which showed antimalarial activity comparable with that of mepacrine when tested against *P. gallinaceum* in chicks. The present work comprises further syntheses of the same type of compound and series of 4-*p*-nitroanilino- and 4-*p*-cyanoanilino-2-aminoalkylamino-6-methylpyrimidines are described. Attention has also been paid to the effects of changes in position of the substituent in the anilino residue, introduction of more than one substituent, and additional substitution in the 5-position of the pyrimidine ring. The dystherapeutic effect of removal of the 6-methyl group now demonstrated for this type of compound is compared with the similar effect noted in Part VII (this vol., p. 378) for the isomeric 2-*p*-substituted-anilino-4-aminoalkylamino-6-methylpyrimidines and discussed.

IN view of the high antimalarial activity exhibited by 4-*p*-chloroanilino-2-γ-di-*n*-butylaminopropylamino-6-methylpyrimidine (I; R′ = Cl, R″ = $[CH_2]_3$·NBu^n_2) described in Part VI (this vol., p. 370) it was thought that compounds of type (I) might repay further study. The investigation has therefore been continued in a number of directions.

(a) *Variations in the dialkylaminoalkylamino group.* The incidence of high antimalarial activity in a compound containing the γ-di-*n*-butylaminopropylamino side chain was so unlike any other known series of antimalarial drugs that it was desirable to see how far activity persisted with less usual types of aminoalkylamino side chains. Reaction of 4-hydroxy-2-methylthio-6-methylpyrimidine with γ-(β′-diethylaminoethoxy)propylamine and γ-*N*-methyl-*N*-β′-diethylaminoethylaminopropylamine and treatment of the resulting 4-hydroxypyrimidines (II; R′ = H, R″ = Me, R‴ = $[CH_2]_3$·O·$[CH_2]_2$·NEt_2) and (II; R′ = H, R″ = Me, R‴ = $[CH_2]_3$·NMe·$[CH_2]_2$·NEt_2) with phosphoryl chloride to give respectively 4-*chloro*-2-γ-(β′-*diethylamino*-

ethoxy)propylamino-6-methylpyrimidine (III; R′ = H, R″ = Me, R‴ = $[CH_2]_3$·O·$[CH_2]_2$·NEt_2) and 4-*chloro*-2-γ-N-*methyl*-N-(β′-*diethylaminoethyl*)*aminopropylamino*-6-*methylpyrimidine* (III; R′ = H, R″ = Me, R‴ = $[CH_2]_3$·NMe·$[CH_2]_2$·NEt_2) followed by condensation of these with *p*-chloroaniline gave compounds of type (I) in which the aminoalkylamino side chain was interrupted by oxygen and nitrogen. Using a similar method 4-p-*chloroanilino*-2-N-*methyl*-N-β-*diethylaminoethylamino*-6-*methylpyrimidine* (IV) was also prepared. For the preparation of 4-p-*chloroanilino*-2-β-*aminoethylamino*-6-*methylpyrimidine* (I; R′ = Cl, R″ = $[CH_2]_2$·NH_2) we had recourse to the second method of synthesis previously worked out for this type of compound (see Part VI, *loc. cit.*) and condensed 2-chloro-4-*p*-chloroanilino-6-methylpyrimidine (VII; R = H) with ethylenediamine. The same compound was also obtained by acid hydrolysis of 4-p-*chloroanilino*-2-β-*acetamidoethylamino*-6-*methylpyrimidine* (I; R′ = Cl, R″ = $[CH_2]_2$·NHAc) prepared by condensation of (VII; R = H) with acetylethylenediamine.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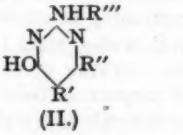
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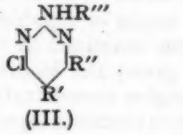
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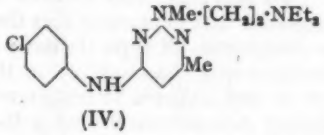
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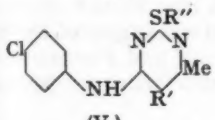
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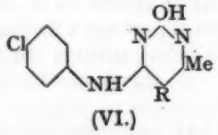
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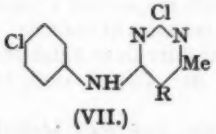
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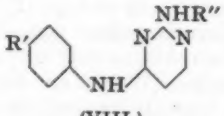

(VIII.)

(b) 4-p-*Nitroanilino*-2-*aminoalkylamino- and* 4-p-*cyanoanilino*-2-*aminoalkylamino*-6-*methylpyrimidines*. Our earlier work (Part VI, *loc. cit.*) on compounds of type (I) showed that 4-*p*-nitroanilino- (I; R′ = NO_2, R″ = $[CH_2]_2$·NEt_2) and 4-*p*-cyanoanilino-2-β-diethylaminoethylamino-6-methylpyrimidine (I; R′ = CN, R″ = $[CH_2]_2$·NEt_2) possessed higher activity against *P. gallinaceum* in chicks than the corresponding *p*-chloroanilino derivative (I; R′ = Cl, R″ = $[CH_2]_2$·NEt_2). As, moreover, replacement of the β-diethylaminoethylamino side chain in (I; R′ = Cl, R″ = $[CH_2]_2$·NEt_2) by certain other dialkylaminoalkylamino side chains led to a pronounced increase in antimalarial activity it was decided to investigate series of compounds of types (I; R′ = NO_2) and (I; R′ = CN) bearing a variety of different aminoalkylamino groups in the 2-position. Accordingly *p*-nitroaniline and *p*-cyanoaniline were each condensed with a variety of intermediates of type (III; R′ = H, R″ = Me, R‴ = aminoalkyl) in aqueous or aqueous acetone solution in presence of hydrochloric acid as catalyst. Details of the compounds prepared are given in Tables II and III.

(c) *Variation of the substituents in the anilino residue.* Although no extensive investigation has been carried out on the effect of changing the position of the substituent in the anilino residue of (I) or of introducing more than one substituent, similar to that recorded in Parts I and II (this vol., pp. 343, 351) for the isomeric 2-*p*-chloroanilino-4-aminoalkylamino-6-methylpyrimidines (IX), these points have received some attention in the present series and the following have been prepared: 4-m-*chloroanilino*-2-γ-*di*-n-*butylaminopropylamino*-, 4-m-*nitroanilino*-2-γ-*piperidinopropylamino*-, 4-(3′ : 4′-*dichloroanilino*)-2-γ-*di*-n-*butylaminopropylamino*-, and 4-(2′ : 4′-*dichloroanilino*)-2-γ-*di*-n-*butylaminopropylamino*-6-*methylpyrimidine*. The biological results (see Table I) indicated, however, that this line of investigation was probably not worth further study.

In the course of this work two compounds containing a *p*-hydroxyanilino residue have been prepared: 4-p-*hydroxyanilino*-2-γ-*diethylaminopropylamino*-6-*methylpyrimidine* (I; R′ = OH, R″ = $[CH_2]_3$·NEt_2) and the corresponding γ-*di*-n-*butylaminopropylamino* derivative (I; R′ = OH, R″ = $[CH_2]_3$·NBu^n_2). The hydroxyl group has not previously been introduced into the pyrimidine antimalarials but its inclusion seemed justified in view of the statement in E.P. 498,752 that certain 8-aminoalkylamino-6-hydroxyquinoline derivatives related to pamaquin have antimalarial activity and the probability that the drug Certuna (*Chem. Zentr.*, 1938, II, 3423; Kikuth, *Klin. Woch.*, 1938, **17**, 524; *Münch. med. Woch.*, 1939, **86**, 362) which received limited clinical trial before the war (Sioli, *Klin. Woch.*, 1938, **17**, 527; Muhlens, *Deut. med. Woch.*, 1938, **64**, 295; Chopra, Das Gupta and Sen, *Indian Med. Gaz.*, 1938, **73**, 667) belongs to this chemical type.

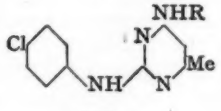
(d) *Variation of the substituents in the 5 and the 6 position.* In Part VII (Curd, Richardson, and Rose, this vol., p. 378) the dystherapeutic effect of removal of the 6-methyl group from the 2-arylamino-4-aminoalkylamino-6-methylpyrimidines of type (IX) was recorded. If, as is suggested in Part VIII (preceding paper), the antimalarial activity of this type of compound is connected with the tautomeric changes which can occur in such a molecule, such a dystherapeutic effect is difficult to interpret and it consequently appeared to be of interest to determine whether removal of the 6-methyl group produces a similar dystherapeutic effect in compounds of type (I).

We therefore prepared 4-p-*chloroanilino*- (VIII; R′ = Cl, R″ = $[CH_2]_3$·NBu^n_2) and 4-p-*nitroanilino*-2-γ-*di*-n-*butylaminopropylaminopyrimidine* (VIII; R′ = NO_2, R″ = $[CH_2]_3$·NBu^n_2). 4-Hydroxy-2-methylthiopyrimidine was condensed with γ-di-*n*-butylaminopropylamine to give (II; R′ = R″ = H, R‴ = $[CH_2]_3$·NBu^n_2) which when treated with phosphoryl chloride afforded 4-*chloro*-2-γ-*di*-n-*butylaminopropylaminopyrimidine* (III; R′ = R″ = H, R‴ = $[CH_2]_3$·NBu^n_2). Reaction of this with *p*-chloroaniline then gave (VIII; R′ = Cl, R″ = $[CH_2]_3$·NBu^n_2) and with *p*-nitroaniline (VIII; R′ = NO_2, R″ = $[CH_2]_3$·NBu^n_2).

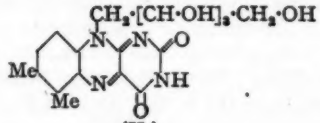
Reference to Table I shows that the antimalarial activity of these compounds is considerably less than that of the corresponding compounds carrying a methyl group in the 6-position. A possible explanation of this, which is applicable not only to compounds of type (I) but also to those of type (IX) and would be reconcilable with any theory relating the antimalarial activity of both types to tautomeric changes, is that the 6-methyl group merely functions as a blocking group. It has been shown (Kelsey *et al.*, *J. Pharm. Exp. Ther.*, 1944, **80**, 391) that quinine is enzymatically altered by the *in vitro* action of rabbit liver to give a degradation product which, as a result of the work of Mead and Koepfli (*J. Biol. Chem.*, 1944, **54**, 507), appears to be derived by the introduction of a hydroxyl group into the α-position of the quinoline nucleus, although no rigid proof of structure is given. It is possible, therefore, that in compounds of types (I) and (IX) the presence of the methyl group in the 6-position merely renders the substances of greater stability *in vivo* than the corresponding unmethylated compounds.

In a previous paper we drew attention to the formal resemblance of compounds of type (I) to riboflavin and suggested that because of this they might be capable of functioning as riboflavin antagonists. Although as yet no compounds of type (I) have been examined as riboflavin antagonists by the *Lactobacillus casei* technique (Madinaveitia, *Biochem. J.*, in the press) Dr. Madinaveitia, working in these laboratories, has demonstrated that *B. coli* adapted to withstand higher concentrations of mepacrine than the normal strain is also protected against 4-*p*-chloroanilino-2-γ-di-*n*-butylaminopropylamino-6-methylpyrimidine. This affords evidence that compounds of type (I) share with mepacrine a common point of attack on *B. coli* which may extend to other micro-organisms including the parasites of malaria. That this is perhaps a flavine enzyme was suggested by the observations that mepacrine inhibits liver aldehyde oxidase (*idem*, private communication) and *d*-amino-acid oxidase (Wright and Sabine, *J. Biol. Chem.*, 1944, **155**, 315). In this case a further modification of compounds of type (I) was indicated.

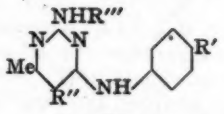
Emerson and Tishler (*Proc. Soc. Exp. Biol. Med.*, 1944, **55**, 184) have demonstrated the riboflavin antagonistic effect of 5 : 6-dimethyl-9-(*d*-1′-ribityl)*iso*alloxazine (*iso*riboflavin) and a comparison of the formula of this compound (X) with 4-arylamino-2-aminoalkylamino-6-methylpyrimidines carrying a 5-alkyl group (XI;



(IX.)



(X.)



(XI.)

R″ = alkyl) revealed a similarity which suggested that the latter might be enhanced riboflavin antagonists and in consequence possess antimalarial properties superior to that of compounds without the 5-alkyl group.

To examine this possibility, 4-chloro-2-ethylthio-5 : 6-dimethylpyrimidine was condensed with *p*-chloroaniline to give 4-p-*chloroanilino*-2-*ethylthio*-5 : 6-*dimethylpyrimidine* (V; R′ = Me, R″ = Et), hydrolysed by boiling with 48% hydrobromic acid to 4-p-*chloroanilino*-2-*hydroxy*-5 : 6-*dimethylpyrimidine* (VI; R = Me), which was then converted by boiling phosphoryl chloride into 2-*chloro*-4-p-*chloroanilino*-5 : 6-*dimethylpyrimidine* (VII; R = Me). Condensation of this with γ-diethylaminopropylamine and γ-dibutylaminopropylamine gave 4-p-*chloroanilino*-2-γ-*diethylaminopropylamino*- (XI; R′ = Cl, R″ = Me, R‴ = $[CH_2]_3$·NEt_2) and 4-p-*chloroanilino*-2-γ-*di*-n-*butylaminopropylamino*-5 : 6-*dimethylpyrimidine* (XI; R′ = Cl, R″ = Me, R‴ = $[CH_2]_3$·NBu^{α}_2), respectively. The preparation of the corresponding 5-ethyl derivatives and a number of related substances is also recorded in the experimental section, but no enhancement of activity resulted.

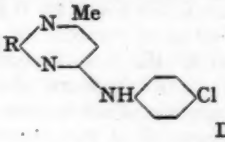
In an attempt to prepare a substance of the same type but containing a group other than alkyl in the 5-position, 4-*chloro*-5-*bromo*-2-*methylthio*-6-*methylpyrimidine* was prepared by the action of phosphoryl chloride

TABLE I.

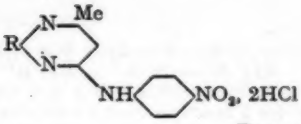
Antimalarial activities.

The antimalarial activities quoted refer to *P. gallinaceum* in chicks and the symbols used to indicate activities have the same meaning as in earlier papers of this series. Detailed biological results will be published elsewhere.

(*a*) Compounds of the type

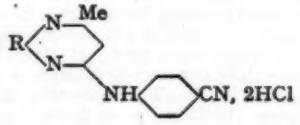


Ref. No.	R.	Dose, mg./kg.	Activity.
5153	NH·$[CH_2]_2$·NMe·$[CH_2]_3$·NEt_2 (trihydrochloride)	240	−
		120	−
5132	NH·$[CH_2]_2$·O·$[CH_2]_3$·NEt_2 (dihydrochloride)	160	−
		80	−
5096	NMe·$[CH_2]_2$·NEt_2	160	−
		80	−
5154	NH·$[CH_2]_2$·NH_2	120	++
		80	+
		40	−

(*b*) Compounds of the type 

Ref. No.	R.	Dose, mg./kg.	Activity.
4950	NH·[CH$_2$]$_3$·NEt$_2$	80	++
		40	+ to ++
		20	±
4631	NH·[CH$_2$]$_3$·N<[CH$_2$]$_4$>CH$_2$	40	++
		20	+ to ++
4630	NH·[CH$_2$]$_3$·NBu^a$_2$	40	+ to ++
		20	+
5094	NH·[CH$_2$]$_3$·NMe$_2$ [1]	80	++
		40	+
5054	NH·CHMe·[CH$_2$]$_3$·NEt$_2$	80	+ to ++
		40	+
5189	NH·[CH$_2$]$_3$·NHBu^a [1]	40	+ to ++
		20	+
5133	NH·[CH$_2$]$_3$·O·[CH$_2$]$_2$·NEt$_2$ [1]	160	++
		80	+

[1] Base.

(*c*) Compounds of the type 

5001	NH·[CH$_2$]$_3$·NEt$_2$	40	+
		20	−
4971	NH·[CH$_2$]$_3$·N<[CH$_2$]$_4$>CH$_2$	80	++
		40	+
5043	NH·[CH$_2$]$_3$·NBu^a$_2$	20	++
5053	NH·CHMe·[CH$_2$]$_3$·NEt$_2$ [2]	160	++
		120	++
		80	±

[2] Dihydrobromide.

(*d*) 4-Arylamino-2-aminoalkylamino-6-methylpyrimidines. Variation of substituents in the anilino residue.

4951	4-*m*-Chloroanilino-2-γ-di-*n*-butylaminopropylamino-6-methylpyrimidine dihydrochloride	120	+
5042	4-*m*-Nitroanilino-2-γ-piperidinopropylamino-6-methylpyrimidine dihydrochloride	160	±
		80	−
5002	4-(3′ : 4′-Dichloroanilino)-2-γ-di-*n*-butylaminopropylamino-6-methylpyrimidine dihydrochloride	40	±
		20	−
5000	4-(2′ : 4′-Dichloroanilino)-2-γ-di-*n*-butylaminopropylamino-6-methylpyrimidine dihydrochloride	80	+
		40	±
4929	4-*p*-Hydroxyanilino-2-γ-diethylaminopropylamino-6-methylpyrimidine dihydrochloride	160	±
		80	−
4930	4-*p*-Hydroxyanilino-2-γ-di-*n*-butylaminopropylamino-6-methylpyrimidine dihydrochloride	160	−
		80	−

(*e*) 4-Arylamino-2-aminoalkylaminopyrimidines. Variation of the substituents in the 5- and 6-positions.

4811	4-*p*-Chloroanilino-2-γ-di-*n*-butylaminopropylamino-pyrimidine dihydrochloride	80	Toxic
		40	−
5049	4-*p*-Nitroanilino-2-γ-di-*n*-butylaminopropylamino-pyrimidine	80	++
		40	±
5004	4-*p*-Chloroanilino-2-γ-di-*n*-butylaminopropylamino-5 : 6-dimethylpyrimidine dihydrochloride	80	+
		40	±
4230	4-*p*-Chloroanilino-2-γ-diethylaminopropylamino-6-methyl-5-ethylpyrimidine dihydrochloride	40	+
		20	−
5050	4-*p*-Nitroanilino-2-γ-diethylaminopropylamino-6-methyl-5-ethylpyrimidine	80	+ to ++
		40	+
		20	−
5051	4-*p*-Cyanoanilino-2-γ-diethylaminopropylamino-6-methyl-5-ethylpyrimidine	80	+ to ++
		40	+ to ++
		20	±
5100	4-*p*-Chloroanilino-2-γ-di-*n*-butylaminopropylamino-6-methyl-5-ethylpyrimidine dihydrochloride	80	++
		40	−
		20	−

on 5-bromo-4-hydroxy-2-methylthio-6-methylpyrimidine (Part VII, *loc. cit.*) and condensed with *p*-chloroaniline to give (V; R′ = Br, R″ = Me) but attempts to hydrolyse the methylthio group in this compound with hydrobromic acid did not give (VI; R = Br) but led to removal of the bromine atom and the formation of 4-*p*-chloroanilino-2-hydroxy-6-methylpyrimidine (VI; R = H).

Experimental.

2-γ-(β′-Diethylaminoethoxy)propylamino-4-hydroxy-6-methylpyrimidine (II; R′ = H, R″ = Me, R‴ = $[CH_2]_3$·O·$[CH_2]_2NEt_2$).—4-Hydroxy-2-methylthio-6-methylpyrimidine (31·2 g.) and γ-(β′-diethylaminoethoxy)propylamine (34·8 g.) were stirred and heated at 150—160° for 3 hours leaving a colourless very viscous oil. It formed a *dipicrate* which crystallised from β-ethoxyethanol in yellow prisms, m. p. 161—163° (Found: C, 42·4; H, 4·3; N, 18·9. $C_{14}H_{26}O_2N_4,2C_6H_3O_7N_3$ requires C, 42·2; H, 4·3; N, 18·9%).

4-Chloro-2-γ-(β′-diethylaminoethoxy)propylamino-6-methylpyrimidine (III; R′ = H, R″ = Me, R‴ = $[CH_2]_3$·O·$[CH_2]_2$·NEt_2).—The above hydroxy compound (56·4 g.) and phosphoryl chloride (100 c.c.) were warmed until reaction occurred. When this had subsided the mixture was refluxed for 10 minutes, cooled, and poured on ice. The clear solution which resulted was made alkaline with sodium hydroxide and extracted with benzene. The benzene was then in turn extracted several times with 5% acetic acid. Addition of sodium hydroxide to the combined acetic acid extracts precipitated an oil which was again taken into benzene and the solution dried. Evaporation left *4-chloro-2-γ-(β′-diethylaminoethoxy)propylamino-6-methylpyrimidine* which was purified by distillation in a vacuum; b. p. 150—152°/0·15 mm. (Found: Cl, 11·7. $C_{14}H_{25}ON_4Cl$ requires Cl, 11·8%). It formed a *dipicrate* which crystallised from β-ethoxyethanol in yellow prisms, m. p. 111—113° (Found: C, 41·2; H, 4·1; N, 18·2. $C_{14}H_{25}ON_4Cl,2C_6H_3O_7N_3$ requires C, 41·1; H, 4·1; N, 18·4%).

4-p-Chloroanilino-2-γ-(β′-diethylaminoethoxy)propylamino-6-methylpyrimidine (I; R′=Cl, R″=$[CH_2]_3$·O·$[CH_2]_2$·NEt_2).—*p*-Chloroaniline (3·2 g.) was added to a solution of the above chloropyrimidine (7·5 g.) in water (25 c.c.) and 10N-hydrochloric acid (2·5 c.c.) and the mixture refluxed for 1 hour. The clear solution obtained was made alkaline with sodium hydroxide and extracted with chloroform. The product was then extracted from the chloroform with 5% acetic acid, and the extract made alkaline and shaken with chloroform. Evaporation of the dried chloroform solution left an oil which gave a *dipicrate*; yellow elongated prisms from β-ethoxyethanol, m. p. 148—150° (Found: C, 45·4; H, 4·0; N, 18·0. $C_{20}H_{30}ON_5Cl,2C_6H_3O_7N_3$ requires C, 45·2; H, 4·2; N, 18·1%). The *dihydrochloride* was prepared by dissolving the base in 2N-hydrochloric acid, evaporating the solution to dryness under reduced pressure, and crystallising the dried residue from alcohol–ethyl acetate. It formed colourless prisms, m. p. 178—180° (Found: C, 50·5; H, 7·7; N, 14·7; Cl′, 14·5. $C_{20}H_{30}ON_5Cl,2HCl,H_2O$ requires C, 49·8; H, 7·0; N, 14·6; Cl′, 14·7%) (5132).

2-γ-N-Methyl-N-(β′-diethylaminoethyl)aminopropylamino-4-hydroxy-6-methylpyrimidine (II; R′ = H, R″ = Me, R‴ = $[CH_2]_3$·NMe·$[CH_2]_2$·NEt_2).—4-Hydroxy-2-methylthio-6-methylpyrimidine (15·6 g.) and *γ-N*-methyl-*N*-(β′-diethylaminoethyl)aminopropylamine (18·75 g.) were heated at 150—160° for 3 hours giving a very viscous oil which afforded a *dipicrate*, purified by crystallisation from β-ethoxyethanol, m. p. 205—207° (decomp.) (Found: C, 43·0; H, 4·7; N, 20·3. $C_{15}H_{29}ON_5,2C_6H_3O_7N_3$ requires C, 43·0; H, 4·6; N, 20·45%).

4-Chloro-2-γ-N-methyl-N-(β′-diethylaminoethyl)aminopropylamino-6-methylpyrimidine (III; R′ = H, R″ = Me, R‴ = $[CH_2]_3$·NMe·$[CH_2]_2$·NEt_2).—The preceding hydroxypyrimidine (29·5 g.) was added to phosphoryl chloride (50 c.c.) and the mixture heated gradually to 100°. When the ensuing vigorous reaction had subsided the mixture was refluxed until a clear solution was obtained (*ca.* 30 mins.). After being cooled, the reaction mixture was poured on ice (250 g.) and the solution made alkaline with sodium hydroxide. The liberated product was taken up in benzene and extracted with 5% acetic acid. Treatment of the acid extract with sodium hydroxide and isolation with chloroform gave the *chloropyrimidine* as an oil, b. p. 142—144°/0·12 mm. (Found: C, 57·7; H, 8·9; N, 22·7. $C_{15}H_{28}N_5Cl$ requires C, 57·4; H, 8·9; N, 22·3%). The *tripicrate* (from β-ethoxyethanol) had m. p. 180—181° (Found: C, 40·0; H, 3·9; N, 19·5. $C_{15}H_{28}N_5Cl,3C_6H_3O_7N_3$ requires C, 39·6; H, 3·7; N, 19·6%).

4-p-Chloroanilino-2-γ-N-methyl-N-(β′-diethylaminoethyl)aminopropylamino-6-methylpyrimidine (I; R = Cl, R″ = $[CH_2]_3$·NMe·$[CH_2]_3$·NEt_2).—A mixture of the above chloropyrimidine (5·2 g.), *p*-chloroaniline (2·1 g.), water (15 c.c.), and 10N-hydrochloric acid (1·5 c.c.) was refluxed for 1 hour, cooled, and worked up as described above for the corresponding γ-diethylaminoethoxypropylamino derivative. The resulting oily base was converted into its *trihydrochloride* by solution in 2N-hydrochloric acid, evaporation of the solution under reduced pressure, and crystallisation of the residue, after drying, from alcohol–ethyl acetate; colourless prisms, m. p. 239—240° (decomp.) (Found: C, 46·9; H, 7·1; N, 16·5; Cl′, 19·7. $C_{21}H_{33}N_6Cl,3HCl,H_2O$ requires C, 47·4; H, 7·1; N, 15·8; Cl′, 20·0%) (5153).

2-N-Methyl-N-β-diethylaminoethylamino-4-hydroxy-6-methylpyrimidine, obtained by heating 4-hydroxy-2-methylthio-6-methylpyrimidine (15·6 g.) with *N*-methyl-*N*-β-diethylaminoethylamine (13 g.) at 140—150° for 3 hours, gave a *dipicrate* which formed yellow prisms and after several crystallisations from methanol had m. p. 167—169° (Found: C, 40·7; H, 4·0; N, 20·3. $C_{12}H_{22}ON_4,2C_6H_3O_7N_3$ requires C, 41·4; H, 4·0; N, 20·1%).

4-Chloro-2-N-methyl-N-β-diethylaminoethylamino-6-methylpyrimidine.—On adding phosphoryl chloride (30 c.c.) to the above hydroxypyrimidine (23·8 g.) reaction occurred immediately. After this had slackened the mixture was refluxed for 15 minutes to give a homogeneous solution. Excess of phosphoryl chloride was then removed under diminished pressure and the residue worked up as described previously for similar compounds. The *chloropyrimidine* was purified by distillation; b. p. 133—135°/0·8 mm. (Found: C, 56·3; H, 8·0; N, 21·4. $C_{13}H_{21}N_4Cl$ requires C, 56·1; H, 8·2; N, 21·8%). It formed a *picrate* which crystallised from methanol in yellow needles, m. p. 144—145° (Found: C, 44·2; H, 5·2; N, 20·1. $C_{13}H_{21}N_4Cl,C_6H_3O_7N_3$ requires C, 44·5; H, 5·0; N, 20·2%).

4-p-Chloroanilino-2-N-methyl-N-β-diethylaminoethylamino-6-methylpyrimidine (IV).—The above chloropyrimidine (9·6 g.), *p*-chloroaniline (4·8 g.), water (40 c.c.), and 10N-hydrochloric acid (3·75 c.c.) were boiled for 1 hour. After cooling, the solid which had separated was filtered off, dissolved in hot water, and reprecipitated with hydrochloric acid. Collected, dried, and crystallised from alcohol, the *dihydrochloride* formed colourless elongated prisms, m. p. 244—246° (Found: C, 50·9; H, 6·6; N, 16·9; Cl′, 17·1. $C_{19}H_{26}N_5Cl,2HCl$ requires C, 51·4; H, 6·7; N, 16·65; Cl′, 16·9%). The *base*, liberated from an aqueous solution of the hydrochloride with sodium hydroxide, crystallised from light petroleum (b. p. 80—100°) in tiny colourless prisms, m. p. 83—85° (Found: C, 62·0; H, 7·5; N, 19·9. $C_{19}H_{26}N_5Cl$ requires C, 62·2; H, 7·5; N, 20·1%) (5096).

4-p-Chloroanilino-2-β-acetamidoethylamino-6-methylpyrimidine (I; R′ = Cl, R″ = $[CH_2]_3$·NHAc).—2-Chloro-4-*p*-chloroanilino-6-methylpyrimidine (6·35 g.) and acetylethylenediamine (3·2 g.) were heated at 120—130° for 8 hours. The melt was dissolved in alcohol and the solution made alkaline with ammonia and poured into water. The precipitated product was filtered off and purified by crystallisation from methanol, forming colourless needles, m. p. 189—191° (Found: C, 56·6; H, 5·9; N, 21·7. $C_{15}H_{18}ON_5Cl$ requires C, 56·3; H, 5·6; N, 21·9%).

4-p-Chloroanilino-2-β-aminoethylamino-6-methylpyrimidine (I; R′ = Cl, R″ = $[CH_2]_3$·NH_2).—(*a*) 2-Chloro-4-*p*-chloroanilino-6-methylpyrimidine (6·35 g.) and ethylenediamine (14 g. of 65%) were heated on the steam-bath for 3 hours and then treated with dilute sodium hydroxide. The resulting solid was collected, dried, and crystallised from ethyl acetate, forming colourless elongated prisms, m. p. 161—163° (Found: C, 56·2; H, 5·8; N, 25·1. $C_{13}H_{16}N_5Cl$ requires C, 56·2; H, 5·8; N, 25·2%) (5154).

(*b*) *4-p*-Chloroanilino-2-β-acetamidoethylamino-6-methylpyrimidine (3 g.), alcohol (20 c.c.), water (10 c.c.), and

Table II. *4-p-Nitroanilino-2-aminoalkylamino-6-methylpyrimidines.*

TABLE II.

4-p-*Nitroanilino*-2-*aminoalkylamino*-6-*methylpyrimidines*.

Substituent at 2.	Procedure.	Derivative.	Solvent used for crystn.; crystalline form.	Melting point.	Formula.	Analysis. Found, %. C.	H.	N.	Cl′.	Required, %. C.	H.	N.	Cl′.
NH·[CH$_2$]$_3$·NEt$_2$	(a)	Dihydrochloride	Dilute alcohol; pale yellow needles	273—275°	$C_{18}H_{26}O_2N_6$,2HCl,0·5H$_2$O	49·5	6·5	—	15·9	49·1	6·6	—	16·1
NH·[CH$_2$]$_3$·N<[CH$_2$]$_4$>CH$_2$		—	Dilute alcohol; yellowish prisms	174—175	$C_{19}H_{26}O_2N_6$,H$_2$O	58·7	7·1	21·9	—	58·8	7·2	21·65	—
	(a)	Dihydrochloride	Dilute alcohol; pale yellow prisms	277—279	$C_{19}H_{26}O_2N_6$,2HCl,2H$_2$O	47·9	6·4	17·8	15·5	47·6	6·7	17·5	14·8
NH·[CH$_2$]$_3$·NBu^a$_2$	(c)	—	Aqueous methanol; yellow prisms	118—119	$C_{22}H_{34}O_2N_6$	63·2	8·1	19·8	—	63·8	8·2	20·3	—
	(d)	Dihydrochloride	Alcohol–ethyl acetate; pale yellow prisms	224—225	$C_{22}H_{34}O_2N_6$,2HCl,1·5H$_2$O	51·7	7·2	16·2	14·2	51·4	7·6	16·3	13·8
NH·[CH$_2$]$_3$·NMe$_2$	(c)	—	Toluene	184	$C_{16}H_{22}O_2N_6$	58·3	6·6	25·5	—	58·2	6·7	25·5	—
NH·CHMe·[CH$_2$]$_3$·NEt		—	Oil										
		Dipicrate	β-Ethoxyethanol; yellow microcrystalline	173—176	$C_{20}H_{30}O_2N_6$,2$C_6H_3O_7N_3$	45·7	4·3	20·4	—	45·5	4·3	19·9	—
	(e)	Dihydrochloride	Alcohol–ethyl acetate; yellow rectangular prisms	*ca.* 116 *	$C_{20}H_{30}O_2N_6$,2HCl,2H$_2$O	48·0	7·3	16·9	14·9	48·5	7·3	17·0	14·4
NH·[CH$_2$]$_3$·NHBu^a	(c)	—	Benzene	141—143	$C_{18}H_{26}O_2N_6$	59·8	7·3	23·6	—	60·3	7·3	23·5	—
NH·[CH$_2$]$_3$·O·[CH$_2$]$_2$·NEt$_2$	(c)	—	Benzene–light petroleum (b. p. 60—80°); yellow prisms	108—109	$C_{20}H_{30}O_3N_6$	59·7	7·2	20·6	—	59·7	7·5	20·9	—

* After being dried in air.

TABLE III.

4-p-*Cyanoanilino*-2-*aminoalkylamino*-6-*methylpyrimidines*.

Substituent at 2.	Procedure.	Derivative.	Solvent used for crystn.; crystalline form.	Melting point.	Formula.	Analysis. Found, %. C.	H.	N.	Cl′.	Required, %. C.	H.	N.	Cl′.
NH·[CH$_2$]$_3$·NEt$_2$	(a)	Dihydrochloride	Alcohol	274—275°	$C_{19}H_{26}N_6$,2HCl,H$_2$O	53·4	7·1	19·3	—	53·1	7·0	19·6	—
NH·[CH$_2$]$_3$·N<[CH$_2$]$_4$>CH$_2$	(a)	Dihydrochloride	Alcohol; colourless needles	280—282	$C_{20}H_{26}N_6$,2HCl,0·5H$_2$O	55·4	6·5	19·0	—	55·5	6·7	19·4	—
NH·[CH$_2$]$_3$·NBu^a$_2$	(a)	Dihydrochloride	Alcohol–ethyl acetate; colourless rectangular prisms	224—226	$C_{23}H_{34}N_6$,2HCl	59·0	7·6	17·9	15·1	59·1	7·7	18·0	15·2
NH·CHMe·[CH$_2$]$_3$·NEt$_2$				B. p. 233—239°/0·15 mm.									
		Dipicrate	β-Ethoxyethanol; flat yellow prisms	199—200	$C_{21}H_{30}N_6$,2$C_6H_3O_7N_3$	48·2	4·4	—	—	48·2	4·4	—	—
	(b)	Dihydrobromide	Alcohol–ethyl acetate; colourless needles	216—220	$C_{21}H_{30}N_6$,2HBr	47·3	5·7	15·7	—	47·7	6·1	15·9	—

hydrochloric acid (10 c.c.) were refluxed for 4 hours. Addition of sodium hydroxide to the cooled solution precipitated the base as an oil which solidified on standing. It was collected, washed, and dried. After crystallisation from ethyl acetate it had m. p. 160—162° either alone or mixed with material made by method (*a*).

Preparation of 4-Arylamino-2-aminoalkylamino-6-methylpyrimidines.—The compounds described in Tables II, III, and IV were made by the following general method. The appropriate 4-chloro-2-aminoalkylamino-6-methylpyrimidine (0·025 g.-mol.) was dissolved in water (50 c.c.), or a mixture of water (40 c.c.) and acetone (10 c.c.) with 10N-hydrochloric acid (3·0 c.c.), the aniline (0·025 g.-mol.) added, and the mixture refluxed for 1—2 hours. Various procedures were used for the isolation of the products and are listed below, reference being made in the tables to the method used for each particular compound. Some of the dihydrochlorides separated on cooling the reaction mixture; these were filtered off, dried, and crystallised [Method (a)]. Where the dihydrochloride did not crystallise out on cooling it was sometimes found convenient to evaporate the reaction mixture to dryness under diminished pressure and to crystallise the residue [Method (b)]. The following method was, however, most commonly adopted. After being cooled, the reaction mixture was made strongly alkaline with sodium hydroxide to liberate the base which was extracted with chloroform and then re-extracted from the chloroform, or from the residue left after evaporation of the chloroform, with 5% acetic acid. Basification of the acid extract then liberated the base which was isolated with chloroform. If the base was obtained as a solid it was purified by vacuum distillation or by crystallisation and used for biological evaluation in this form [Method (c)]. Where the base was obtained as an oil it was usually characterised as its dipicrate and then converted into its dihydrochloride (or dihydrobromide) by dissolving in warm 2N-acid. Sometimes the salt separated on cooling and was filtered off and dried [Method (d)]. Otherwise the solution was evaporated to dryness under reduced pressure at 50—60° and the dried residue crystallised [Method (e)].

*2-γ-Di-*n*-butylaminopropylamino-4-hydroxypyrimidine* (II; R′ = R″ = H, R‴ = $[CH_2]_3$·NBu^n_2).—4-Hydroxy-2-methylthiopyrimidine (17 g.) (Wheeler and Merriam, *Amer. Chem. J.*, 1903, **29**, 478) and γ-di-*n*-butylaminopropylamine (22·3 g.) were heated at 170° for 2 hours. The product, left as a highly viscous oil on cooling, formed a *dipicrate* which crystallised from β-ethoxyethanol, m. p. 198—199° (Found: C, 44·3; H, 4·7; N, 18·4. $C_{15}H_{28}ON_4,2C_6H_3O_7N_3$ requires C, 43·9; H, 4·6; N, 19·0%).

4-Chloro-2-γ-di-*n*-butylaminopropylaminopyrimidine (III; R′ = R″ = H, R‴ = $[CH_2]_3$·NBu^n_2), prepared from the above hydroxy compound with phosphoryl chloride, followed by working up in the usual way, formed a viscous oil. The *dipicrate* crystallised from β-ethoxyethanol, m. p. 150—151° (Found: C, 43·4; H, 4·6; N, 17·9. $C_{15}H_{27}N_4Cl,2C_6H_3O_7N_3$ requires C, 42·8; H, 4·4; N, 18·5%).

*4-p-Chloroanilino-2-γ-di-*n*-butylaminopropylaminopyrimidine* (VIII; R′ = Cl, R″ = $[CH_2]_3$·NBu^n_2).—A mixture of 4-chloro-2-γ-di-*n*-butylaminopropylaminopyrimidine (7·5 g.), *p*-chloroaniline (3·2 g.), water (25 c.c.), and 10N-hydrochloric acid (2·5 c.c.) was refluxed for 1 hour and then evaporated to dryness under reduced pressure. The residue was dried by dissolving in alcohol and again evaporating to dryness. It was then crystallised from alcohol–ethyl acetate and gave colourless prisms of the *dihydrochloride*, m. p. 155—157° (Found: C, 53·2; H, 7·3; Cl′, 14·4. $C_{21}H_{32}N_5Cl,2HCl,0·5H_2O$ requires C, 53·4; H, 7·4; Cl′, 15·0%) (4811).

*4-p-Nitroanilino-2-γ-di-*n*-butylaminopropylaminopyrimidine* (VIII; R′ = NO_2, R″ = $[CH_2]_3$·NBu^n_2).—*p*-Nitroaniline (3·9 g.) was added to a solution of 4-chloro-2-γ-di-*n*-butylaminopropylaminopyrimidine (8·4 g.) in water (28 c.c.) and 10N-hydrochloric acid (2·8 c.c.), and the mixture refluxed for 1 hour. The cooled solution was made alkaline with sodium hydroxide, and the liberated product separated and dissolved in 5% acetic acid. After treatment with decolorising charcoal the acetic acid solution was treated with sodium hydroxide and extracted with chloroform. Evaporation of the dried extract gave the *base* which crystallised from benzene–light petroleum (b. p. 60—80°) in yellow prisms, m. p. 112—114° (Found: C, 62·8; H, 7·3; N, 21·0. $C_{21}H_{32}O_2N_6$ requires C, 63·0; H, 8·0; N, 21·0%) (5049). Its *dipicrate* separated from β-ethoxyethanol in yellow plates, m. p. 206—207° (Found: C, 46·1; H, 4·5. $C_{21}H_{32}O_2N_6,2C_6H_3O_7N_3$ requires C, 46·2; H, 4·4%).

4-p-Chloroanilino-2-ethylthio-5 : 6-dimethylpyrimidine (V; R′ = Me, R″ = Et).—A mixture of 4-chloro-2-ethylthio-5 : 6-dimethylpyrimidine (Chi and Kao, *J. Amer. Chem. Soc.*, 1936, **58**, 767) (10·1 g.), *p*-chloroaniline (6·4 g.), water (40 c.c.), acetone (10 c.c.), and 10N-hydrochloric acid (0·5 c.c.) was refluxed for 2 hours, cooled, and filtered. The collected solid was dissolved in alcohol with the addition of ammonia to give an alkaline reaction, the solution diluted with water, and the precipitated product isolated by filtration. After being washed with water it was crystallised from alcohol, forming colourless needles, m. p. 165—166° (Found: S, 10·9. $C_{14}H_{16}N_3ClS$ requires S, 10·9%) (yield, 8·2 g.).

4-p-Chloroanilino-2-hydroxy-5 : 6-dimethylpyrimidine (VI; R = Me).—The above ethylthiopyrimidine (10 g.) and 48% hydrobromic acid (100 c.c.) were refluxed for 40 hours and the resulting clear solution diluted with water and made alkaline with ammonia. The precipitated *4-p-chloroanilino-2-hydroxy-5 : 6-dimethylpyrimidine* was filtered off and dried (yield, 8·2 g.). Crystallised from β-ethoxyethanol–alcohol it formed colourless thick prisms, m. p. 305—310° (decomp.) with previous marked darkening (Found: N, 16·8; Cl, 13·8. $C_{12}H_{12}ON_3Cl$ requires N, 16·8; Cl, 14·2%).

2-Chloro-4-p-chloroanilino-5 : 6-dimethylpyrimidine (VII; R = Me).—*4-p*-Chloroanilino-2-hydroxy-5 : 6-dimethylpyrimidine (29 g.) was treated with boiling phosphoryl chloride (65 c.c.) during 3 hours. After removal of the excess of phosphoryl chloride under diminished pressure the residue was treated with ice and water. After standing for some time the mixture was made alkaline with ammonia and the solid collected. Crystallisation from alcohol gave the *chloropyrimidine* as colourless prisms, m. p. 173—174° (yield, 19·8 g.) (Found: C, 53·9; H, 4·0; N, 15·8. $C_{12}H_{11}N_3Cl_2$ requires C, 53·7; H, 4·1; N, 15·7%).

4-p-Chloroanilino-2-γ-diethylaminopropylamino-5 : 6-dimethylpyrimidine (XI; R′=Cl, R″=Me, R‴=$[CH_2]_3$·NEt_2).—2-Chloro-4-*p*-chloroanilino-5 : 6-dimethylpyrimidine (10 g.) and γ-diethylaminopropylamine (6 g.) were heated at 120—130° for 8 hours. The melt was then dissolved in warm dilute hydrochloric acid, and the solution made alkaline with sodium hydroxide and extracted with chloroform. The chloroform was extracted several times with 5% acetic acid, the extracts combined and added to excess of sodium hydroxide solution. The *base*, isolated by extraction with chloroform, crystallised from light petroleum (b. p. 60—80°); colourless prisms, m. p. 64—65° (Found: C, 60·1; H, 7·5; N, 18·6. $C_{19}H_{28}N_5Cl,H_2O$ requires C, 60·1; H, 7·9; N, 18·4%). The *dipicrate* crystallised from β-ethoxyethanol in yellow prisms, m. p. 175—176° (Found: C, 46·1; H, 4·5; N, 18·5. $C_{19}H_{28}N_5Cl,2C_6H_3O_7N_3$ requires C, 45·4; H, 4·1; N, 18·8%).

4-*p*-Chloroanilino-2-γ-di-*n*-butylaminopropylamino-5 : 6-dimethylpyrimidine (XI; R′ = Cl, R″ = Me, R‴ = $[CH_2]_3$·NBu^n_2), prepared in a similar manner using γ-di-*n*-butylaminopropylamine, was obtained as an oil. This gave a *dipicrate* which separated from β-ethoxyethanol–alcohol in yellow needles, m. p. 188—190° (Found: C, 47·9; H, 4·8; N, 17·3. $C_{23}H_{36}N_5Cl,2C_6H_3O_7N_3$ requires C, 48·0; H, 4·8; N, 17·6%) and a *dihydrochloride* (5004) which crystallised from alcohol–ethyl acetate and formed colourless needles, m. p. 204—205° (Found: C, 55·3; H, 7·4; N, 14·4; Cl′, 14·5. $C_{23}H_{36}N_5Cl,2HCl,0·5H_2O$ requires C, 55·3; H, 7·8; N, 14·0; Cl′, 14·2%).

4-Chloro-5-bromo-2-methylthio-6-methylpyrimidine.—5-Bromo-4-hydroxy-2-methylthio-6-methylpyrimidine (Part VII; *loc. cit.*) (20 g.) and phosphoryl chloride (65 c.c.) were refluxed for 1 hour. After removal of excess of phosphoryl chloride the residue was poured on ice and made alkaline with ammonia. The *chloropyrimidine* solidified on standing and was

TABLE IV.

4-Arylamino-2-aminoalkylamino-6-methylpyrimidines. Variation of the substituent in the anilino residue.

Substituent at 2.	Substituent at 4.	Procedure.	Derivative.	Solvent used for crystn.; crystalline form.	Melting point.	Formula.	Analysis. Found, %. C.	H.	N.	Cl.	Required, %. C.	H.	N.	Cl.
NH·	NH·[CH$_2$]$_3$·NBu^n$_2$	(d)	Dipicrate	β-Ethoxyethanol–alcohol; thick yellow lamina	180—181°	$C_{32}H_{42}N_8Cl_2,2C_6H_3O_7N_3$	46·7	4·6	17·8	—	47·4	4·5	17·9	—
			Dihydrochloride	Butanol–ethyl acetate; thick colourless prisms	221—223	$C_{32}H_{42}N_8Cl_2,2HCl,0·5H_2O$	54·4	7·4	15·0	14·4	54·4	7·6	14·4	14·6
NH·	NH·[CH$_2$]$_3$·N<[CH$_2$]$_5$>CH$_2$	(d)	Dihydrochloride	Alcohol–water; colourless prisms	262—264	$C_{19}H_{32}O_2N_6,2HCl,1·5H_2O$	48·8	6·2	17·5	15·3	48·5	6·6	17·9	15·1
NH·	NH·[CH$_2$]$_3$·NBu^n$_2$		Dipicrate	β-Ethoxyethanol–alcohol; thick yellow lamina	192—193	$C_{32}H_{42}N_8Cl_2,2C_6H_3O_7N_3$	45·5	4·4	17·2	—	45·5	4·4	17·2	—
		(a)	Dihydrochloride	Methanol–ethyl acetate; colourless prisms	240—242	$C_{32}H_{42}N_8Cl_2,2HCl,H_2O$	50·1	7·2	13·1	12·8	49·9	7·0	13·2	13·4
NH·	NH·[CH$_2$]$_3$·NBu^n$_2$	(c)	—	—	50—52 (b. p. 220—222°/ 0·12 mm.)	$C_{32}H_{42}N_8Cl_2$	60·0	7·3	15·7	—	60·3	7·5	16·0	—
			Dipicrate	β-Ethoxyethanol	226—227°	$C_{32}H_{42}N_8Cl_2,2C_6H_3O_7N_3$	45·7	4·6	16·6	—	45·5	4·4	17·2	—
NH·	NH·[CH$_2$]$_3$·NEt$_2$	(b)	Dihydrochloride	Aqueous alcohol; colourless needles	269—271	$C_{15}H_{31}ON_5,2HCl$	53·6	7·2	17·1	17·7	53·7	7·2	17·4	17·7
NH·	NH·[CH$_2$]$_3$·NBu^n$_2$	(b)	Dihydrochloride	Alcohol–ethyl acetate	120—122	$C_{23}H_{45}ON_5,2HCl,2H_2O$	53·2	8·0	14·2	14·2	53·4	8·3	14·2	14·3

then filtered off, pressed as dry as possible, and dissolved in benzene. After being dried, the benzene solution was evaporated and the residue crystallised from light petroleum (b. p. 60—80°); colourless needles, m. p. 72—73° (Found: S, 12·8. $C_6H_6N_2ClBrS$ requires S, 12·6%).

5-Bromo-4-p-chloroanilino-2-methylthio-6-methylpyrimidine (V; R′ = Br, R″ = Me).—4-Chloro-5-bromo-2-methylthio-6-methylpyrimidine (6·3 g.), *p*-chloroaniline (3·2 g.), water (20 c.c.), acetone (5 c.c.), and 10N-hydrochloric acid (0·25 c.c.) were refluxed for 3 hours. On cooling, the oily layer which had formed solidified. After filtration, it was dissolved in alcohol, and the solution made alkaline with ammonia and then diluted with water to precipitate the product. Crystallised from aqueous methanol it formed colourless blunt-ended needles, m. p. 116—117° (Found: C, 42·1; H, 3·5; N, 12·5. $C_{12}H_{11}N_3ClBrS$ requires C, 41·8; H, 3·2; N, 12·2%).

Hydrolysis of 5-Bromo-4-p-chloroanilino-2-methylthio-6-methylpyrimidine.—The methylthio compound (10 g.) was boiled with hydrobromic acid (100 c.c. of 48%) for 22 hours and the solution was then diluted with water and made alkaline with ammonia. The precipitated product was collected, washed with water, and dried. In view of its low solubility in solvents it was purified in the following manner. Sodium hydroxide was added to a suspension in alcohol and the mixture raised to the boil. After treatment with decolorising carbon the solution was filtered and cooled. The sodium salt which separated was filtered off and suspended in alcohol, and the suspension acidified with acetic acid and diluted with water. The precipitated product was filtered off, washed with water, and dried; m. p. >340° (Found: C, 56·3; H, 4·2; N, 17·8; Cl, 15·1. $C_{11}H_{10}ON_3Cl$ requires C, 56·05; H, 4·25; N, 17·8; Cl, 15·1%). The product was thus 4-*p*-chloroanilino-2-hydroxy-6-methylpyrimidine (VI; R = H). This was confirmed by conversion into the corresponding chloro compound (VII; R = H) with phosphoryl chloride; 2-chloro-4-*p*-chloroanilino-6-methylpyrimidine was thus obtained, m. p. 135—137° undepressed in admixture with authentic material (Part VI, *loc. cit.*).

2-γ-Diethylaminopropylamino-4-hydroxy-6-methyl-5-ethylpyrimidine (II; R′ = Et, R″ = Me, R‴ = $[CH_2]_3$·NEt_2).—4-Hydroxy-2-methylthio-6-methyl-5-ethylpyrimidine (Wheeler and Merriam, *Amer. Chem. J.*, 1903, **29**, 489) (36·8 g.) and γ-diethylaminopropylamine (26 g.) were heated to 130°. Evolution of methylthiol took place rapidly at this temperature and appeared to be complete after ½ hour. The temperature was then raised to 160° and this temperarure maintained for 2 hours to ensure complete reaction. On cooling, the product remained as an extremely viscous oil which could not be crystallised. The *dipicrate* formed yellow prisms from alcohol, m. p. 191—192° (Found: N, 19·1. $C_{14}H_{26}ON_4,2C_6H_3O_7N_3$ requires N, 19·3%).

4-Chloro-2-γ-diethylaminopropylamino-6-methyl-5-ethylpyrimidine (III; R′ = Et, R″ = Me, R‴ = $[CH_2]_3$·NEt_2).—To the above hydroxy compound (53·2 g.) phosphoryl chloride (100 c.c.) was added at 25°. A vigorous reaction took place. When this had subsided the mixture was boiled for 2 minutes, cooled, and poured on ice with stirring. The resulting clear solution was immediately made strongly alkaline with sodium hydroxide, the temperature being kept below 40°, and the product extracted with benzene (4 extractions). The combined benzene extracts were washed with water and then shaken several times with 5% acetic acid. The product, liberated from the acid extracts with sodium hydroxide, was again extracted with benzene and the benzene solution washed twice with water, dried, and evaporated. The residual oil was distilled giving *4-chloro-2-γ-diethylaminopropylamino-6-methyl-5-ethylpyrimidine* as a colourless oil, b. p. 138°/0·1 mm. Its *dipicrate* crystallised from β-ethoxyethanol in yellow prisms, m. p. 160—161° (Found: C, 41·8; H, 4·5; N, 19·0; Cl, 4·6. $C_{14}H_{25}N_4Cl,2C_6H_3O_7N_3$ requires C, 42·0; H, 4·2; N, 18·9; Cl, 4·8%).

4-p-Chloroanilino-2-γ-diethylaminopropylamino-6-methyl-5-ethylpyrimidine
(XI; R′ = Cl, R″ = Et, R‴ = $[CH_2]_3$·NEt_2).

—4-Chloro-2-γ-diethylaminopropylamino-6-methyl-5-ethylpyrimidine (8·5 g.), *p*-chloroaniline (11·5 g.), and *p*-chloroaniline hydrochloride (4·9 g.) were mixed and heated in an oil-bath at 170—175° for 2 hours. Repeated extraction of the cooled reaction mixture with hot benzene left the *dihydrochloride* which crystallised from methanol in colourless laminæ, m. p. 245—246° (Found: C, 53·5; H, 6·7; N, 15·6; Cl′, 15·6. $C_{20}H_{30}N_5Cl,2HCl$ requires C, 53·5; H, 7·1; N, 15·6; Cl′, 15·8%) (4230).

4-p-Nitroanilino-2-γ-diethylaminopropylamino-6-methyl-5-ethylpyrimidine
(XI; R′ = NO_2, R″ = Et, R‴ = $[CH_2]_3$·NEt_2).

—4-Chloro-2-γ-diethylaminopropylamino-6-methyl-5-ethylpyrimidine (7·1 g.), *p*-nitroaniline (3·45 g.), water (25 c.c.), and 10N-hydrochloric acid (2·5 c.c.) were refluxed for 1 hour, the resulting solution was cooled and made alkaline with sodium hydroxide. The precipitated base was taken into chloroform and then extracted with 5% acetic acid. The acid extract was treated with sodium hydroxide and the product isolated with chloroform. It separated from light petroleum (b. p. 100—120°) in yellow prisms, m. p. 126—128° (Found: C, 62·4; H, 7·6; N, 21·8. $C_{20}H_{30}O_2N_6$ requires C, 62·2; H, 7·8; N, 21·8%) (5050).

4-p-Cyanoanilino-2-γ-diethylaminopropylamino-6-methyl-5-ethylpyrimidine
(XI; R′ = CN, R″ = Et, R‴ = $[CH_2]_3$·NEt_2).

—A mixture of (III; R′ = Et, R″ = Me, R‴ = $[CH_2]_3$·NEt_2) (7·1 g.), *p*-cyanoaniline (3·0 g.), water (25 c.c.), and 10N-hydrochloric acid (2·5 c.c.) was refluxed for 1 hour, and the solution cooled and made alkaline with sodium hydroxide. The product was precipitated as an oil which soon solidified. It was filtered off and purified by dissolution in 5% acetic acid and reprecipitation with sodium hydroxide. Crystallised from aqueous alcohol, *4-p-cyanoanilino-2-γ-diethylaminopropylamino-6-methyl-5-ethylpyrimidine* formed colourless prisms, m. p. 151—152° (Found: C, 68·7; H, 8·3; N, 23·1. $C_{21}H_{30}N_6$ requires C, 68·8; H, 8·2; N, 23·0%) (5051).

2-γ-Di-n-butylaminopropylamino-4-hydroxy-6-methyl-5-ethylpyrimidine (II; R′=Et, R″=Me, R‴=$[CH_2]_3$·NBu^n_2).—γ-Di-*n*-butylaminopropylamine (8·2 g.) and 4-hydroxy-2-methylthio-6-methyl-5-ethylpyrimidine (8·3 g.) were mixed and fused at 160—170° for 2 hours leaving a highly viscous oil. With picric acid (one equivalent) it gave a *monopicrate* which crystallised from methanol; yellow prisms, m. p. 182—183° (Found: C, 52·5; H, 6·8; N, 17·5. $C_{18}H_{34}ON_4,C_6H_3O_7N_3$ requires C, 52·3; H, 6·7; N, 17·8%). The *dipicrate* was obtained by adding an alcoholic solution of picric acid (excess) to a solution of the base in β-ethoxyethanol. Crystallised from alcohol it formed stout yellow needles, m. p. 166—167° (Found: C, 46·2; H, 5·1; N, 18·4. $C_{18}H_{34}ON_4,2C_6H_3O_7N_3$ requires C, 46·15; H, 5·1; N, 17·9%).

4-Chloro-2-γ-di-n-butylaminopropylamino-6-methyl-5-ethylpyrimidine
(III; R′ = Et, R″ = Me, R‴ = $[CH_2]_3$·NBu^n_2).

—The above hydroxypyrimidine (6·2 g.) and phosphoryl chloride (25 c.c.) were warmed until reaction occurred. After this had subsided the mixture was refluxed for 2 minutes and worked up as in the preparation of the γ-diethylaminopropylamino derivative. The chloropyrimidine was thus obtained as an oil which was used for the following condensation without distillation. The *dipicrate* crystallised from methanol in flat yellow needles, m. p. 140—141° (Found: C, 45·1; H, 5·0; N, 17·5; Cl, 4·7. $C_{18}H_{33}N_4Cl,2C_6H_3O_7N_3$ requires C, 45·1; H, 4·9; N, 17·5; Cl, 4·4%).

4-p-Chloroanilino-2-γ-di-n-butylaminopropylamino-6-methyl-5-ethylpyrimidine
(XI; R′ = Cl, R″ = Et, R‴ = $[CH_2]_3$·NBu^n_2).

—The above chloropyrimidine (4·0 g.), *p*-chloroaniline (4·4 g.), and *p*-chloroaniline hydrochloride (1·9 g.) were mixed and fused at 160—170° for 2 hours. The resulting liquid reaction mixture was poured into benzene (1 l.) and the mixture

boiled for 5 minutes. The solid product obtained was filtered off and crystallised from methanol–ethyl acetate giving the *dihydrochloride*, m. p. 215—216° (Found: C, 56·7; H, 7·6; N, 13·9; Cl′, 14·3. $C_{24}H_{38}N_8Cl,2HCl$ requires C, 57·1; H, 7·9; N, 13·9; Cl′, 14·1%) (5100).

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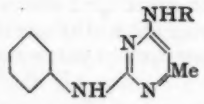
149. *Synthetic Antimalarials. Part X. Some Aryl-diguanide ("-biguanide") Derivatives.*

By F. H. S. CURD and F. L. ROSE.

The relation between antimalarial activity and the chemical constitution of the pyrimidine compounds described in earlier papers in this series has been studied and a working hypothesis has been advanced which led to the synthesis of and discovery of activity in a series of diguanides ("biguanides"). One derivative, N^1-*p*-chlorophenyl-N^5-*iso*propyldiguanide ("Paludrine") has been examined extensively in human malaria.

IN Part I (Curd and Rose, this vol., p. 343) the discovery was recorded of a new class of antimalarial drugs typified by structure [I; R = alkylene·N(alkyl)$_2$]. The phenyl nucleus carried a variety of substituents.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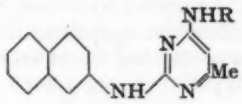
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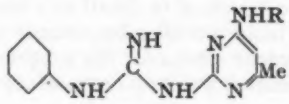
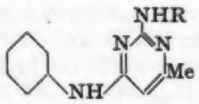

(III.)

In subsequent papers it was shown how this type had been elaborated to provide yet other active structures, as (II), (III) and (IV), again with the nucleus variously substituted. The suggestion was made, supported in part by the work of our colleague Dr. Madinaveitia (*Biochem. J.*, in press), that these substances might be func-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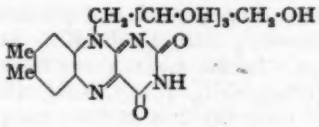
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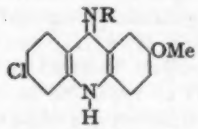
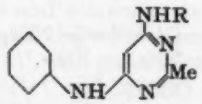
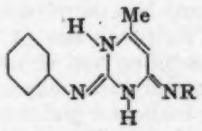
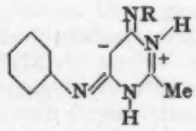

(VI.)

tioning as plasmodicidal agents by virtue of their antagonism for riboflavin (V) to which they could be shown to bear some formal structural resemblance. Attempts have been made to enhance the antimalarial activity by introducing substituents into (I), *e.g.*, 3 : 4-dimethyl into the benzene ring (Part II, this vol., p. 351) and 5-methyl into the pyrimidine nucleus (Part VII, this vol., p. 378), with the object of still further increasing the similarity to riboflavin. The results obtained have been inconclusive and, while we do not dismiss the possible validity of the antagonism hypothesis, we have returned as a means of extending our researches to one of the early arguments on which the new antimalarial drugs were in part based, namely, consideration of the tautomeric possibilities existing within certain known active drug molecules. This line of thought also provided a rational means for further simplifying drug structure and thus facilitating the elucidation of the ultimate relation between chemical constitution and biological activity. In earlier papers we have referred to the hypothesis presented by Schönhöfer (*Z. physiol. Chem.*, 1942, **274**, 1) which seeks to relate antimalarial activity in the mepacrine molecule to the possible formation of a *p*-quinonoid tautomer involving the ring nitrogen atom and the 5-alkylamino group in the manner shown in (VI). Reference to types (I) and (IV) shows that a similar *p*-quinonoid structure is only possible in the former, yet both provide active substances. We therefore tentatively modified the Schönhöfer hypothesis to embrace tautomerism leading to an *o*-quinonoid structure and concluded that, in the pyrimidine series, antimalarial activity might be expected when both arylamino and alkylamino substituents were present each of which permitted the formulation of either *o*- or *p*-quinonoid-like tautomers. The inactivity of the isomeric type (VII) (see Part VIII, this vol., p. 717) called for some modification of this

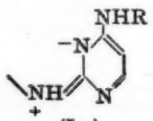

(VII.)

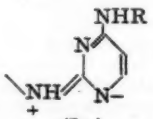

(VIII.)

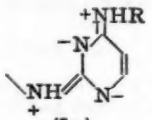

(IX.)

generalisation, and it was further postulated that the tautomeric systems associated with the substituent arylamino and alkylamino groups should be capable of independent function. In (VII) the tautomeric systems

are interdependent in that, for example, positioning of the bonds in the RNH—C═N— system in the manner formulated prevents tautomerism elsewhere in the molecule. Without listing all the possibilities inherent in types (I), (IV), and (VII), this point can be further illustrated by referring to tautomer (VIII) which has no equivalent amongst the variants of (VII), except the unlikely (IX). The guanidine (III) is similar to (I) and in fact introduces still another system, that of the guanidine linkage, capable of tautomeric modification. In addition to the prototropic changes inherent in the molecules now being considered, a like number of resonance possibilities are conceivable. Thus, the pyrimidine moiety of (I) may be a hybrid between the several zwitterion forms (IA)—(IE) and the " Kékulé " forms. Here again there are limitations in type (VII) not to be found in types (I), (III), or (IV). To what extent prototropy or resonance, or both, are associated with antimalarial


(IA.)


(IB.)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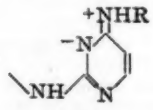
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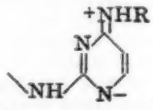
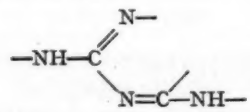
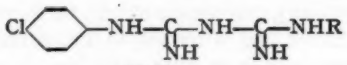

(IE.)

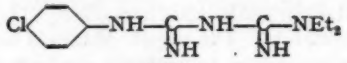
activity, it was not at this stage possible to indicate. These properties would be influenced by changes in the molecule, such as the introduction of substituents into the benzene ring, or replacement of amino hydrogen by alkyl. Much of the work subsequent to that described here has been devoted to a study of these aspects and will be discussed in detail at a later date. For the moment we accepted the principles enunciated above as the basis for a working hypothesis. Further consideration suggested that while a pyrimidine ring provided a convenient means for the synthesis of structures containing the salient features, a ring system *per se* need not be essential, and any heteroenoid system of the type



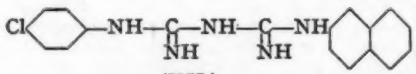
might be expected to function in the same manner.

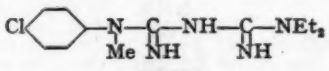
The diguanide (" biguanide ") molecule, in which we had previously been interested for the synthesis of compounds of type (III) (see Part IV, this vol., p. 362), provided the necessary structural features around which we might expect to build up active drugs. Initial research was therefore directed towards the preparation of compounds of type (X) in which R=$[CH_2]_2$·NEt_2, $[CH_2]_3$·NEt_2, and CHMe·$[CH_2]_3$·NEt_2. The preparative methods employed are discussed below. Only the first of these compounds was examined in detail; it proved quite inactive. We have been unable to explain this result, but at the time it was attributed to the highly basic character of the molecule, and the possible influence on tautomerism and resonance of the ionic charges that it would carry under physiological conditions. To minimise any such effect, one of the basic groups was omitted and simpler molecules typified by (XI) were synthesised. These proved markedly active and the research


(X.)


(XI.)

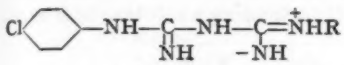
then became an investigation of the effect of variation in the aryl substituents and the terminal alkyl groups. Constitutions and antimalarial activities are given in the table on p. 733. It was found that a wide range of mono- and di-alkyl derivatives corresponding to (X) and (XI) were active, highest activity occurring with a total of 3 or 4 carbon atoms in the alkyl groups with a maximum at mono-*iso*propyl (X; R = Pr^{β}). The parent *p*-chlorophenyldiguanide and its monomethyl derivative were ineffective. An important feature of these compounds was that their biological activity was not confined to the erythrocytic forms of the malarial parasite. This point is discussed elsewhere in detail (Curd, Davey, and Rose, *Ann. Trop. Med. Parasit.*, 1945, **39**, 208), but briefly it has been found by Dr. Davey that many of these substances act on a parasite phase preceding the blood-invasive form, that is, in experimental species at least, they function as true causal prophylactic agents. Replacement of the alkyl group by a further aryl residue to give, *e.g.*, (XII) greatly reduces the antimalarial effect, as does also the introduction of a methyl group as in (XIII). The influence of the

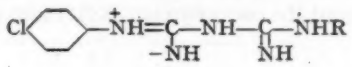

(XII.)

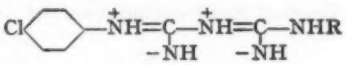

(XIII.)

substituent in the benzene ring appeared to be similar to that observed in the earlier pyrimidine drugs, chlorine in the *para* position being the most effective of the few variants examined. Reviewing, in the light of these results, the premises relating to resonance and tautomerism which led to the preparation and examination of the diguanide drugs, it is apparent that some differentiation of the two effects may

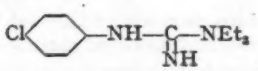
become possible. Structure (X) can be formulated in seven " zwitterion " modifications [compare (IA)—(IE)] of which (XA), (XB), and (XC) are examples and the same number of possibilities exists for the di- and

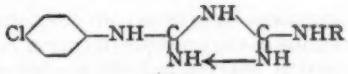

(XA.)


(XB.)


(XC.)

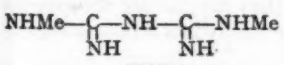
tri-alkyl derivatives such as (XI) and (XIII), active and almost inactive respectively. The number of possible tautomerides available through prototropy is dependent, however, on the degree of alkylation of the diguanide chain, and it may be significant that in the feebly active (XIII) the positioning of the alkyl groups does not permit the existence of the molecule of the two independent tautomeric systems originally postulated as essential for antimalarial activity. Similar limitations apply to the simple guanidine (XIV) which is inactive. A further feature of the diguanide structure which has to be considered is the possibility that the molecule may be modified by hydrogen bonding, leading to cyclic structures such as (XV), the existence of which may profoundly influence biological properties.

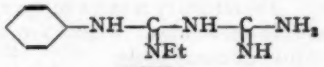

(XIV.)

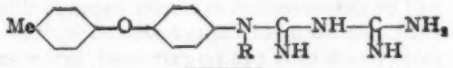

(XV.)

Several of the compounds described in this paper have been examined in human malaria. Clinical details will be published elsewhere by the workers concerned, but it may be said here that (X; R = Pr^{β}), for example, for which the name " Paludrine " has been registered, has proved highly effective at doses lower than those customary with mepacrine and quinine.

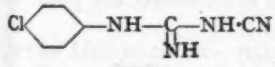
The synthesis of diguanide and its simple alkyl and aryl derivatives has been fairly extensively studied by other workers. The most convenient starting material has been dicyandiamide. This substance by interaction with ammonium chloride yields diguanide hydrochloride (Bamberger and Dieckmann, *Ber.*, **1892**, **25**, 545; Smolka and Friedreich, *Montash.*, 1888, **9**, 228) and Smolka and Friedreich have extended the reaction to arylamines and alkylamines. The use of ammoniacal copper sulphate solution appears to facilitate the reaction with ammonia and allows diguanide to be isolated as its sparingly soluble copper complex (Rathke, *Ber.*, 1879, **12**, 780; Herth, *Ber.*, 1880, **13**, 1358; Rackmann, *Annalen*, 1910, **376**, 170). Slotta and Tschesche (*Ber.*, 1929, **62**, 1394) showed that dicyanimide could be made to react with two molecules of an alkylamine hydrochloride, *e.g.*, methylamine hydrochloride, to give (XVI), but, so far as we are aware, the only example of a disubstituted diguanide bearing an aryl group and an alkyl group on different nitrogen atoms has been provided by Cramer (*Ber.*, 1901, **34**, 2602) who caused *N*-phenyl-*N'*-ethylthiourea to react with guanidine in the presence of mercuric oxide to yield (XVII). An aryldiguanide (XVIII; R = NH·$[CH_2]_2$·NEt_2) has been described by I.G. Farbenind. (D.R.-P. 632,572/1933) and said *inter alia* to exhibit plasmodicidal and antibacterial

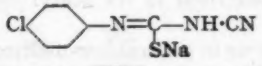

(XVI.)

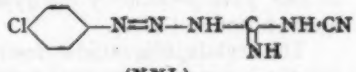

(XVII.)


(XVIII.)

properties. The parent *p*-chlorophenyldiguanide corresponding to (X) has been described by us (Part IV, *loc. cit.*) and by Strukov, Sychra, and Smirnov (*J. Chem. Ind.* (U.S.S.R.), **1941**, **18**, 22), and was made by reaction of *p*-chloroaniline hydrochloride with dicyandiamide. We considered that an analogous reaction between *p*-chlorophenyldicyandiamide (XIX) and a dialkylaminoalkylamine would provide the most satisfactory route to (X; R = dialkylaminoalkyl). Other routes have subsequently been examined and many have proved successful. These will be recorded in later papers in this series. Phenyldicyandiamide was first prepared by

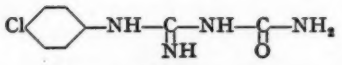

(XIX.)


(XX.)

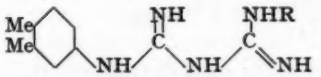

(XXI.)

Wheeler and Jamieson (*J. Amer. Chem. Soc.*, **1903**, **25**, 719) from (XXI), the reaction product of phenyl *iso*thiocyanate and sodium cyanamide, by *S*-methylation and treatment with ammonia, but a more convenient preparation of the same compound and (XIX) was described by Walther and Grieshammer (*J. pr. Chem.*, **1915**, **92**, 251) who passed dry hydrogen chloride into an ether suspension of (XXI), and the corresponding phenyl, *m*-tolyl, and *p*-tolyl compounds, and eliminated nitrogen from the products by adding them to hot water. (XXI) is obtained in good yield by coupling diazotised *p*-chloroaniline with dicyandiamide in aqueous sodium carbonate, but we have found it dangerous to handle in bulk when dry, since it is readily detonated by friction. The Walther and Grieshammer method has been modified therefore by employing the method described by Rose and Broadbent (E.P. Appln. 8888/44) in which the more stable wet filter paste from the coupling reaction is decomposed smoothly and cleanly by addition to a mixture of concentrated hydrochloric acid and

a water-miscible solvent, such as β-ethoxyethanol, acetic acid, or acetone. The reaction was effected at temperatures between 20° and 40° and was usually complete in 2 hours. The aryldicyandiamide was then isolated by adding water and purified by reprecipitation from an aqueous solution of the sodium salt. Walther and Grieshammer (*loc. cit.*) record the conversion of (XXI) into (XXII) by heating a solution in ethanol



(XXII.)



(XXIII.)

and hydrogen chloride (used either as dry gas or as the concentrated aqueous solution), but it is not clear whether hydrolysis of the cyano group preceded or followed elimination of the azo-nitrogen. The modified reaction conditions have been used to prepare, in addition to (XIX), the phenyl, *p*-nitrophenyl, *p*-tolyl, *p*-anisyl, *p*-acetamidophenyl, and 3 : 4-xylyl derivatives. The last named was employed since the resultant diguanides (XXIII), formulated as shown, could still be remotely related to riboflavin (V) although less obviously than (I).

The aryldicyandiamides have been converted into diguanides by interaction with either (*a*) the amine hydrochloride, or (*b*) the amine in the presence of copper sulphate. The first method was used mainly with the aromatic amines, and the reaction, effected in boiling aqueous dioxan or β-ethoxyethanol, was in many cases rapidly completed. Aliphatic amines reacted much more slowly under these conditions and it was found more convenient to employ the second method with excess of free amine dissolved in aqueous ethanol, with addition of one equivalent of copper sulphate calculated on the dicyandiamide used. The diguanide was then obtained as a copper complex which in many cases remained dissolved in the hot reaction mixture. The rate of conversion into diguanide could be judged by the formation of the coloured complex (purple-brown). It was extremely rapid with certain amines, notably dimethylamine, but with the primary amines such as ethylamine a reaction period of 4—24 hours was necessary. In the earliest experiments, the copper compound was precipitated by the addition of water to the cooled reaction mixture. It was then dissolved in dilute hydrochloric acid, the copper removed as the sulphide, and the acid filtrate made alkaline with sodium hydroxide. The use of ammonia in place of sodium hydroxide failed to throw out many of the strongly basic diguanides. In other instances the sparingly soluble hydrochlorides were precipitated. The latter effect could also be obtained with sodium hydroxide if added slowly. Where it was desired to isolate free base with certainty, the acid filtrate was added in a thin stream to an excess of sodium hydroxide solution. In later experiments it was found that, after precipitation of the diguanide copper complex from the initial reaction mixture, a considerable amount of diguanide remained in the aqueous ethanolic filtrate, and the procedure was modified in that either before or after addition of water the excess of ethanol was distilled off, and the resultant suspension was made acid and then worked up without isolation of the copper complex. Copper bronze powder was used in place of copper sulphate in one experiment. The copper complex was found to have been formed as an intermediate and the ultimate yield of diguanide was of the usual order. The exact constitutions of the copper derivatives are now being investigated and they will be characterised in a later paper in this series. Preliminary results suggest that they are chelate compounds with one atom of copper shared by two diguanide molecules. Many are soluble in hydrocarbon solvents, from which they can be extracted, however, by dilute mineral acids.

On the assumption that facile reaction of a cyanamide or dicyandiamide with an amine requires the latter to be present as the ion, the use of the free amine would not be expected to provide good yields of the diguanide. Experience has confirmed this in general, but in certain instances a demonstrable yield of diguanide has been obtained, *e.g.*, with piperidine. This can be attributed to the acidic character of (XIX) which provided the necessary salt formation with the amine for ion production.

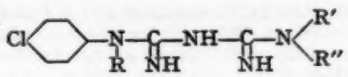
The N^1-methylated diguanides (XIII) were prepared from the corresponding N^1-*p*-chlorophenyl-N^1-methyldicyandiamide. The latter was obtained from (XIX) and methyl sulphate. Reaction was normal with diethylamine and *iso*propylamine in the presence of copper sulphate, but ammonia and ammonium chloride at 150° gave *p*-chloro-*N*-methylaniline, characterised as its acetyl derivative, thus establishing the point of methylation in (XIX).

The arylalkyldiguanides described above were in general low-melting solids, sparingly soluble in cold water, but the lower members were sufficiently soluble to impart a strongly alkaline reaction to their solutions. They have not all been characterised as the free bases since some were not solid at laboratory temperature, and many rapidly absorbed carbon dioxide from the atmosphere. The salts formed with an equivalent of acid, such as the acetates or hydrochlorides, were stable and crystalline and the diguanides were frequently isolated in this form. Physical measurements have indicated the presence of a second basic group in the molecule, but details of this work, together with other results arising from an extensive study of the physical properties of the diguanide drugs, will be recorded in a later communication.

Antimalarial Activities.

The test method was that described by Curd, Davey, and Rose (*loc. cit.*) using *P. gallinaceum* in chicks. The activity at various doses is indicated either as inactive (−), slight (+), marked (++), or very high (+++). The drugs were administered orally.

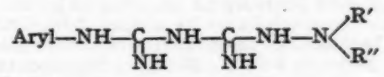
(1.)



Formula of Diguanide.

Reference No.	R.	R′.	R″.	Dose, mg./kg.	Activity.
3374	H	$[CH_2]_2{\cdot}NEt_2$	H	250	−
—	H	$[CH_2]_3{\cdot}NEt_2$	H	—	*
5114	H	$CHMe{\cdot}[CH_2]_3{\cdot}NEt_2$	H	—	*
4172	H	$[CH_2]_2{\cdot}NEt_2$	Et	200	−
3327	H	H	H	125	−
5093	H	Me	H	80	−
4134	H	Me	Me	80	−
4967	H	Et	H	20	++
3926	H	Et	Et	80	++
4094	Me	Et	Et	160	+
4887	H	Pr^{α}	H	20	+++
4888	H	Pr^{β}	H	10	+++
4329	H	Pr^{α}	Me	40	++
4430	H	Pr^{β}	Me	16	+++
5393	Me	Pr^{β}	H	—	*
4968	H	$CH_2{\cdot}CH{:}CH_2$	H	20	++
4565	H	Bu^{α}	H	80	++
4567	H	Bu^{β}	H	320	+
4568	H	Bu^{γ}	H	40	++
4095	H	Bu^{α}	Bu^{α}	200 400	− +
4635	H	$C_5H_{11}{}^{\alpha}$	H	80	++
5596	H	$CH<[CH_2]_4>CH_2$	H	—	*
4204	H	$[CH_2]_4 = R'R''$		80	+
3926	H	$[CH_2]_5 = R'R''$		80	−
5157	H	$[CH_2]_2{\cdot}O{\cdot}[CH_2]_2 = R'R''$		40	−
5234	H	OMe	H	80	−
4171	H	Me	$[CH_2]_2{\cdot}OMe$	160	−

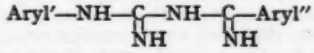
(2.)



Formula of Diguanide.

Reference No.	Aryl.	R′.	R″.	Dose, mg./kg.	Activity.
4461	Ph	Me	Pr^{β}	—	*
4210	Ph	Et	Et	160	−
4492	Ph	Bu^{α}	Bu^{α}	160	−
4175	p-C_6H_4Me	Me	Me	200	−
4969	3 : 4-$C_6H_3Me_2$	Et	Et	200 80	+ −
4174	p-$C_6H_4{\cdot}OMe$	Me	Me	200	−
4125	p-$C_6H_4{\cdot}OMe$	Et	Et	120	−
3781	p-$C_6H_4{\cdot}OMe$	$[CH_2]_5 = R'R''$		200	+
—	p-$C_6H_4{\cdot}NO_2$	Me	Me	—	*
4376	p-$C_6H_4{\cdot}NO_2$	Et	Et	80	+
4566	p-$C_6H_4{\cdot}NHAc$	Me	Pr^{β}	80	−

(3.)



Formula of Diguanide.

Reference No.	Aryl′.	Aryl″.	Dose, mg./kg.	Activity.
4202	Ph	Ph	80	−
—	p-C_6H_4Cl	Ph	—	*
4123	p-C_6H_4Cl	p-$C_6H_4{\cdot}OMe$	120	−
4970	p-C_6H_4Cl	$C_{10}H_7{}^{\beta}$	80	+
4124	p-$C_6H_4{\cdot}OMe$	p-$C_6H_4{\cdot}OMe$	200	−
—	p-C_6H_4Me	p-C_6H_4Me	—	*

Compounds marked * had not been tested at the time of going to press.

Experimental.

Phenyldicyandiamide derivatives.

Phenyldicyandiamide.—Aniline (23 g.) was diazotised at 5° in 2·5N-hydrochloric acid (250 c.c.) with sodium nitrite (17·5 g. in 100 c.c. of water) and added to dicyandiamide (23 g.) in water (700 c.c.) at 20°. Excess of 10N-sodium hydroxide was added to maintain a strong alkaline reaction, and after ½ hour the golden-yellow solution was acidified with acetic acid. The precipitated triazene was filtered off, washed with water, partly dried by suction on the filter, and added during ½ hour to a mixture of β-ethoxyethanol (200 c.c.) and 10N-hydrochloric acid (28 c.c.) stirred at 28—30°. After 1

hour no more nitrogen was evolved. Water (500 c.c.) was added and the crude precipitate of phenyldicyandiamide was collected, dissolved in boiling N-sodium hydroxide (250 c.c.), treated with charcoal, and reprecipitated, after filtration, with dilute hydrochloric acid. The dry crystalline solid (20 g.) gave colourless needles from methanol, m. p. 196—197°. Wheeler and Jamieson (*loc. cit.*) give m. p. 190—191°.

p-*Acetamidophenyldicyandiamide*.—Similarly prepared from *p*-aminoacetanilide, the intermediate triazene being decomposed at 34°, mineral acidity neutralised with sodium acetate after dilution of the reaction mixture, and purification *via* the sodium salt omitted. The crude product crystallised from water yielded the *compound* in colourless plates, m. p. 234—235° (decomp.) (Found: N, 29·3. $C_{10}H_{11}ON_5,H_2O$ requires N, 29·8%).

3 : 4-*Xylyldicyandiamide*.—Similarly prepared from 3 : 4-xylidine, but using three times as much β-ethoxyethanol and decomposition of the triazene at 42°. The *compound* formed colourless prisms from β-ethoxyethanol, m. p. 217·5—218° (Found: N, 29·55. $C_{10}H_{12}N_4$ requires N, 29·8%).

p-*Tolyldicyandiamide*.—Similarly prepared from *p*-toluidine. Colourless crystals from methanol, m. p. 211·5—212·5°. Walther and Grieshammer (*loc. cit.*) give m. p. 207—208°.

p-*Anisyldicyandiamide*.—Similarly prepared from *p*-anisidine. The *compound* formed colourless plates from methanol, m. p. 188—189° (Found: N, 29·35. $C_9H_{10}ON_4$ requires N, 29·45%).

p-*Nitrophenyldicyandiamide*.—Sodium nitrite (36 g.) in water (100 c.c.) was added rapidly to the suspension obtained by adding a solution of *p*-nitroaniline (70 g.) in boiling 4N-hydrochloric acid (350 c.c.) to crushed ice (850 g.) and water (400 c.c.). The diazo solution was stirred with dicyandiamide (84 g.) in water (2·2 l.) and ice to maintain it at 0°, 10N-sodium hydroxide being added to give a strong alkaline reaction. After 1 hour, common salt (800 g.) was stirred in and the precipitated sodium salt of the triazene was filtered off, washed with brine, and dried at 40°. It was cautiously crushed and added during 20 minutes to a stirred mixture of β-ethoxyethanol (400 c.c.) and 10N-hydrochloric acid (100 c.c.) kept at 30—34°. Stirring was continued for a further 1½ hours at 25—32° and, after addition of water (300 c.c.) and treatment with charcoal, the mixture was filtered. Nearly pure p-*nitrophenyldicyandiamide* (22 g.) was precipitated on further dilution of the filtrate with water (3 l.); it crystallised from aqueous β-ethoxyethanol in pale yellow prisms, m. p. 243—244° (Found: C, 46·8; H, 3·2; N, 33·95. $C_8H_7O_2N_5$ requires C, 46·8; H, 3·4; N, 34·1%).

p-*Chlorophenyldicyandiamide* (XIX).—The suspension obtained by cooling a solution of *p*-chloroaniline (128 g.) in hot 5N-hydrochloric acid (500 c.c.) was diazotised by adding sodium nitrite (70 g.) in water (200 c.c.), and added to dicyandiamide (92 g.) dissolved in water (2·8 l.) at 20°. Anhydrous sodium carbonate was added during 1½ hours to maintain an alkaline reaction and the suspension was then filtered off. The washed and pressed triazene was added during ½ hour to a stirred mixture of β-ethoxyethanol (500 c.c.) and 10N-hydrochloric acid (112 c.c.) at 33—36°. After ½ hour, water (4·5 l.) was added and the crystalline precipitate collected, washed, and dried. The crude *p*-chlorophenyldicyandiamide (150 g.) had m. p. 192—194°; after purification as described above for the phenyl derivative the product (108 g.) had m. p. 200—202°; recrystallised from ethanol it formed colourless needles, m. p. 202·5—203°. Walther and Grieshammer (*loc. cit.*) give m. p. 197—198°.

N^1-p-*Chlorophenyl*-N^1-*methyldicyandiamide*.—Methyl sulphate (25 c.c.) in methanol (25 c.c.) was added during 20 minutes to *p*-chlorophenyldicyandiamide (19·5 g.) dissolved in methanol (50 c.c.) and 10N-sodium hydroxide (37 c.c.) stirred at 15—20°. After 1 hour water (250 c.c.) was added, and the precipitate collected and dried. The crude product, extracted with hot benzene (100 c.c.) and re-precipitated by adding light petroleum (50 c.c.), gave 5·2 g., m. p. 160—164°, which, recrystallised from water, yielded the *compound* in colourless needles, m. p. 166—168° (Found: C, 51·4; H, 4·4; N, 26·2. $C_9H_9N_4Cl$ requires C, 51·7; H, 4·3; N, 26·8%). The orientation of the methyl group was determined by heating the chlorophenylmethyldicyandiamide (3 g.) in β-ethoxyethanol (5 c.c.) with ammonia (*d* 0·88, 2·5 c.c.) and ammonium chloride (1·5 g.) for 14 hours in a sealed tube at 150°. The contents of the tube were acidified with hydrochloric acid, the solvent was distilled off under reduced pressure, and the oil formed on adding sodium hydroxide was extracted with ether. The residue after evaporation of the ether was heated with acetic anhydride in acetic acid; water was added and the solution then evaporated to dryness. The oily residue solidified on cooling and was washed on to a filter with water and dried. Yield, 1·65 g., m. p. 71—85°. After recrystallisation twice from light petroleum it gave colourless needles, m. p. 90·5—91·5° not depressed by admixture with an authentic specimen of *p*-chloro-*N*-methylacetanilide made by acetylation of *p*-chloro-*N*-methylaniline itself obtained by hydrolysis in boiling sulphuric acid (60%) of p-*chloro*-N-*methyltosylanilide*. The last named substance [needles from light petroleum, m. p. 92·5—93·5° (Found: Cl, 11·7; S, 11·1. $C_{14}H_{14}O_2NClS$ requires Cl, 12·0; S, 10·8%)] was formed by slow addition of methyl sulphate (5 mol.) to p-*chlorotosylanilide* [from *p*-chloroaniline and the theoretical amount of tosyl chloride in pyridine at 100° for 1 hour; colourless prisms from benzene, m. p. 118—119° (Found: C, 55·55; H, 4·35; S, 12·8. $C_{13}H_{12}O_2NClS$ requires C, 55·4; H, 4·25; S, 12·6%)], kept dissolved in water at 85—90° by additions of 10N-sodium hydroxide.

Diguanides.

N^1-p-*Chlorophenyl*-N^5-*β-diethylaminoethyldiguanide*, (X; R = $[CH_2]_2{\cdot}NEt_2$) (3374).—*p*-Chlorophenyldicyandiamide (XX, 15 g.), β-ethoxyethanol (15 c.c.), β-diethylaminoethylamine (13 c.c.), and copper sulphate pentahydrate (9 g.) in water (18 c.c.), were refluxed with stirring for 2 hours. The semi-solid left by decantation after diluting with water (250 c.c.) was dissolved in N-hydrochloric acid (300 c.c.) and a concentrated aqueous solution of sodium sulphide nonahydrate (15 g.) stirred in. Decolourising charcoal was added and the copper sulphide filtered off. The solid obtained by adding excess of sodium hydroxide to the filtrate was collected and dried (14 g.), m. p. 126—128°. From light petroleum (b. p. 100—120°) the *compound* formed colourless needles, m. p. 137—139° (Found: N, 26·75. $C_{14}H_{23}N_6Cl$ requires N, 27·0%).

N^1-p-*Chlorophenyl*-N^5-*γ-diethylaminopropyldiguanide* (X; R = $[CH_2]_3{\cdot}NEt_2$).—Similarly prepared from *p*-chlorophenyldicyandiamide and γ-diethylaminopropylamine, decantation from the initial reaction product being omitted, this was obtained as an oil which when extracted by ether, dried (KOH), and crystallised from light petroleum gave the *compound* as hygroscopic colourless prisms, m. p. 81—83° (Found: Cl, 11·1. $C_{15}H_{25}N_6Cl$ requires Cl, 10·9%).

N^1-p-*Chlorophenyl*-N^5-*δ-diethylamino-α-methylbutyldiguanide* (X; R = $CHMe{\cdot}[CH_2]_3{\cdot}NEt_2$) (5114).—*p*-Chlorophenyldicyandiamide (19·5 g.), ethanol (150 c.c.), δ-diethylamino-α-methylbutylamine (19 g.), and copper sulphate pentahydrate (12·5 g.) in water (60 c.c.), were refluxed with stirring for 20 hours. The semi-solid precipitate, formed on adding water (500 c.c.) to the purple solution, redissolved on adding 10N-hydrochloric acid (50 c.c.). Sodium sulphide nonahydrate (40 g.) in concentrated aqueous solution was added, the copper sulphide filtered off, and the filtrate made strongly alkaline with sodium hydroxide. The semi-solid precipitate was washed several times by decantation with water and the diguanide finally freed from excess of amine reactant by stirring with copper sulphate (25 g.) dissolved in excess dilute ammonia, to convert it into the insoluble copper complex. This was washed well with water, redissolved in dilute hydrochloric acid, decomposed as before with sodium sulphide, and the sticky precipitate formed after adding sodium hydroxide dried in a vacuum over sodium hydroxide for 4 days. The resultant glassy solid could not be induced to crystallise, but the diguanide was obtained as the *carbonate* (13·8 g.), m. p. 78—80° (decomp.) (Found: C, 52·4; H, 8·15; N, 20·85. $C_{17}H_{29}N_6Cl,H_2CO_3$ requires C, 52·1; H, 7·5; N, 20·3%), by passage of carbon dioxide into a solution of the base in acetone (200 c.c.) and water (1 c.c.).

N¹-p-*Chlorophenyl*-N⁵-*β-diethylaminoethyl*-N⁵-*ethyldiguanide* (4172).—*p*-Chlorophenyldicyandiamide (9·5 g.), ethanol (50 c.c.), *β*-diethylaminoethylethylamine (20 c.c.), and copper sulphate (6·25 g.) in water (30 c.c.), were refluxed with stirring for ½ hour. The copper complex, precipitated by adding water (250 c.c.), was collected, redissolved in 1·5N-hydrochloric acid (300 c.c.), and decomposed with sodium sulphide (20 g.) as described above. The crude oily diguanide obtained by adding sodium hydroxide to the acid filtrate was converted into the hydrochloride by passing dry hydrogen chloride into a solution in ether previously dried (KOH). The hydrochloride was dissolved in water and made alkaline with sodium hydroxide, and the solid base collected and dried in a vacuum over sodium hydroxide. The *hemihydrate* was obtained as colourless needles, m. p. 78·5—79·5°, from light petroleum (b. p. 100—120°) (Found: C, 55·95; H, 7·25; N, 24·0. $C_{16}H_{27}N_5Cl,\frac{1}{2}H_2O$ requires C, 56·0; H, 8·05; N, 24·15%).

N¹-p-*Chlorophenyl*-N⁵-*methyldiguanide* (X; R = Me) (5093).—Prepared as described for 5114, from *p*-chlorophenyldicyandiamide (9·7 g.) and methylamine (20% aqueous solution, 30 c.c.), the mixture being refluxed for 1½ hours and reconversion to the copper complex omitted. The crude base (6·6 g.) was redissolved in water (75 c.c.) and sufficient hydrochloric acid at 40°, treated with charcoal, and the filtrate made faintly alkaline with dilute ammonia. On cooling, the *hydrochloride* crystallised out; it recrystallised from water (40 c.c.) in colourless needles (3·6 g.), m. p. 227—228° (Found: C, 41·0; H, 4·75; N, 26·35. $C_9H_{13}N_5Cl,HCl$ requires C, 41·2; H, 4·95; N, 26·7%). The base obtained by adding sodium hydroxide to a solution of the hydrochloride gave colourless needles from toluene, m. p. 85—86°, but no satisfactory analytical figures were obtained because of the rapidity with which it absorbed carbon dioxide from the atmosphere.

N¹-p-*Chlorophenyl*-N⁵ : N⁵-*dimethyldiguanide* (4134).—Similarly prepared from *p*-chlorophenyldicyandiamide (9·5 g.) and dimethylamine (20% aqueous solution, 40 c.c.) by an almost instantaneous reaction. The *base* formed colourless plates (5·0 g.) from toluene, m. p. 169° (Found: C, 50·0; H, 5·45; N, 28·9. $C_{10}H_{14}N_5Cl$ requires C, 50·0; H, 5·8; N, 29·1%).

N¹-p-*Chlorophenyl*-N⁵-*ethyldiguanide* (X; R = Et) (4967).—Similarly prepared from *p*-chlorophenyldicyandiamide (9·7 g.) and ethylamine (30% aqueous solution, 12 c.c.), the mixture being refluxed for 16 hours. The copper complex was not isolated, but, before it was decomposed, the ethanol was distilled off. The crude base, purified by reprecipitation by sodium hydroxide from a solution in cold dilute acetic acid, was finally isolated as the *acetate* (7·5 g.) by addition of glacial acetic acid (2·6 c.c.) to a solution in acetone (100 c.c.); colourless crystals, m. p. 160—161° (Found: C, 47·85; H, 5·95; N, 23·4. $C_{10}H_{14}N_5Cl,CH_3{\cdot}CO_2H$ requires C, 48·1; H, 6·0; N, 23·35%). The *base*, obtained from the acetate by treatment with sodium hydroxide, gave colourless prisms from benzene, m. p. 113—114° (Found: C, 49·6; H, 6·0; N, 29·85. $C_{10}H_{14}N_5Cl$ requires C, 50·0; H, 5·8; N, 29·1%).

N¹-p-*Chlorophenyl*-N⁵ : N⁵-*diethyldiguanide* (XI) (3936).—Similarly prepared using diethylamine (10 c.c.). The *base* formed colourless needles from light petroleum (b. p. 100—120°), m. p. 133—134° (Found: C, 53·6; H, 7·05; N, 25·9. $C_{12}H_{18}N_5Cl$ requires C, 53·6; H, 6·7; N, 26·1%).

N¹-p-*Chlorophenyl*-N¹-*methyl*-N⁵ : N⁵-*diethyldiguanide* (XIII) (4094).—Prepared as described for (X; R = Me) from *p*-chlorophenylmethyldicyandiamide (9·8 g.) and diethylamine (100%, 10 c.c.), and isolated as the *hydrochloride* by making the solution obtained after filtration from the copper sulphide just alkaline with ammonia. Recrystallisation from water gave colourless prisms, m. p. 182—184° (Found: C, 46·5; H, 6·7; N, 20·45; Cl′, 10·7. $C_{13}H_{20}N_5Cl,HCl,H_2O$ requires C, 46·4; H, 6·8; N, 20·8; Cl′, 10·6%).

N¹-p-*Chlorophenyl*-N⁵-n-*propyldiguanide* (X; R = Pr$^\alpha$) (4887).—Prepared as described for (X; R = Et) from *p*-chlorophenyldicyandiamide (9·5 g.) and *n*-propylamine (15 c.c.). The *acetate* was obtained as colourless prisms, m. p. 164—165° (Found: C, 49·85; H, 5·85; N, 22·6. $C_{11}H_{18}N_5Cl,CH_3{\cdot}CO_2H$ requires C, 49·75; H, 6·35; N, 22·3%), and the *base* as colourless prisms from aqueous ethanol, m. p. 58·5—60° (Found: C, 48·55; H, 6·05; N, 26·2. $C_{11}H_{18}N_5Cl,\frac{1}{2}H_2O$ requires C, 48·4; H, 6·6; N, 25·8%).

N¹-p-*Chlorophenyl*-N⁵-iso*propyldiguanide* (X; R = Pr$^\beta$) (4888).—Similarly prepared from *p*-chlorophenyldicyandiamide (9·5 g.) and *iso*propylamine (15 c.c.). The *acetate* was obtained as colourless needles from ethanol, m. p. 184—185° (Found: C, 48·4; H, 6·1; N, 21·85. $C_{11}H_{18}N_5Cl,CH_3{\cdot}CO_2H,\frac{1}{2}H_2O$ requires C, 48·35; H, 6·5; N, 21·7%), and the *base* as colourless rectangular plates from toluene, m. p. 129° (Found: C, 51·95; H, 6·2; N, 27·1. $C_{11}H_{18}N_5Cl$ requires C, 52·0; H, 6·3; N, 27·6%). The *hydrochloride*, obtained by the method described for (XIII), formed colourless needles from water, m. p. 243—244° (Found: Cl′, 12·8. $C_{11}H_{18}N_5Cl,HCl$ requires Cl′, 12·6%).

N¹-p-*Chlorophenyl*-N⁵-*methyl*-N⁵-n-*propyldiguanide* (4329).—Prepared as described for 4172, using methyl *n*-propylamine (7 c.c.), the mixture being refluxed for 5 hours. The crude *base* (6·5 g.) obtained after decomposition of the copper complex yielded colourless plates from toluene, m. p. 125—126° (Found: C, 54·15; H, 6·6; N, 25·8. $C_{12}H_{18}N_5Cl$ requires C, 53·7; H, 6·7; N, 26·1%).

N¹-p-*Chlorophenyl*-N⁵-*methyl*-N⁵-iso*propyldiguanide* (4430).—Similarly prepared from methyl *iso*propylamine (20 c.c.). The crude *base* (9·4 g.) yielded colourless needles from toluene, m. p. 174—175° (Found: C, 53·7; H, 6·95; N, 25·65. $C_{12}H_{18}N_5Cl$ requires C, 53·7; H, 6·7; N, 26·1%); the *acetate* had m. p. 212° (Found: C, 51·5; H, 6·6; N, 21·3. $C_{12}H_{18}N_5Cl,CH_3{\cdot}CO_2H$ requires C, 51·3; H, 6·7; N, 21·35%).

N¹-p-*Chlorophenyl*-N¹-*methyl*-N⁵-iso*propyldiguanide* (5393).—Prepared as described for (XIII) from *p*-chlorophenylmethyldicyandiamide (7·5 g.) and *iso*propylamine (5 c.c.) and isolated as the *base*, which formed colourless prisms from light petroleum (b. p. 100—120°), m. p. 98—100° (Found: N, 25·7. $C_{13}H_{19}N_5Cl$ requires N, 26·1%). The *hydrochloride* (from acetone) formed colourless prisms from ethanol, m. p. 229—230° (Found: C, 47·75; H, 5·7; N, 23·1. $C_{13}H_{19}N_5Cl,HCl$ requires C, 47·6; H, 6·25; N, 23·0%).

N¹-p-*Chlorophenyl*-N⁵-*allyldiguanide* (X; R = $CH_2{\cdot}CH{:}CH_2$) (4968).—Prepared as described for (X; R = Et) and isolated as the *base*, which formed colourless prisms from toluene, m. p. 99—101° (Found: C, 52·2; H, 5·7; N, 27·5. $C_{11}H_{14}N_5Cl$ requires C, 52·5; H, 5·55; N, 27·8%).

N¹-p-*Chlorophenyl*-N⁵-n-*butyldiguanide* (X; R = Bu$^\alpha$) (4565).—Prepared as described for 4172 using *n*-butylamine (10 c.c.), the mixture being refluxed for 16 hours. The crude base could not well be crystallised, but formed an *acetate* in acetone, colourless prisms (6·2 g.), m. p. 158° (Found: C, 52·0; H, 6·75; N, 21·15; $C_{13}H_{19}N_5Cl,CH_3{\cdot}CO_2H$ requires C, 51·3; H, 6·7; N, 21·4%). The *hydrochloride*, obtained by making slightly alkaline with ammonia a solution of the base in excess of dilute hydrochloric acid, formed colourless prisms from water, m. p. 208° (Found: Cl′, 11·4. $C_{13}H_{19}N_5Cl,HCl$ requires Cl′, 11·7%).

N¹-p-*Chlorophenyl*-N⁵-iso*butyldiguanide* (X; R = Bu$^\beta$) (4567).—Prepared similarly from *iso*butylamine (10 c.c.). The base formed an acetate in acetone, colourless leaflets (4·5 g.), m. p. 166—167°, and a *hydrochloride*, colourless plates from ethanol, m. p. 233—235·5° (Found: C, 47·25; H, 6·1; N, 23·2; Cl′, 12·1. $C_{13}H_{19}N_5Cl,HCl$ requires C, 47·3; H, 6·2; N, 23·0; Cl′, 11·7%).

N¹-p-*Chlorophenyl*-N⁵-tert.-*butyldiguanide* (X; R = Bu$^\gamma$) (4568).—Prepared similarly from *tert.*-butylamine (10 c.c.). The base formed a *hydrochloride* (1·7 g.) in acetone, colourless prisms from ethanol, m. p. 232—234° depressed in admixture with the hydrochloride from (X, R = Bu$^\beta$) (Found: N, 22·95; Cl′, 11·8. $C_{13}H_{19}N_5Cl,HCl$ requires N, 23·0; Cl′, 11·7%).

N¹-p-*Chlorophenyl*-N⁵ : N⁵-*di*-n-*butyldiguanide* (4095).—Prepared as described for 4172, using dibutylamine, the mixture being refluxed for 3 hours. The copper complex was decomposed by stirring with N-sulphuric acid (500 c.c.) which

left the sparingly soluble diguanide *sulphate*, colourless prisms from aqueous ethanol, m. p. 180—182° (Found: C, 50·8; H, 6·9; N, 18·1. $C_{16}H_{26}N_5Cl,\frac{1}{2}H_2SO_4$ requires C, 51·5; H, 7·2; N, 18·7%). The more soluble acetate, m. p. 156°, was employed in the antimalarial test.

N¹-p-*Chlorophenyl*-N⁵-n-*amyldiguanide* (X; R = C_5H_{11}[a]) (4635).—Prepared as described for (X; R = Me) from *n*-amylamine (10 c.c.), the mixture being refluxed for 20 hours. The *hydrochloride*, isolated as described for that of (X, R = Me), formed colourless needles (4·6 g.) from water, m. p. 229° (Found: C, 49·15; H, 6·5; N, 21·45. $C_{12}H_{20}N_5Cl,HCl$ requires C, 49·0; H, 6·6; N, 22·0%).

N¹-p-*Chlorophenyl*-N⁵-cyclo*hexyldiguanide* (X; R = C_6H_{11}).—Prepared as described for (X; R = $[CH_2]_2{\cdot}NEt_2$) from *p*-chlorophenyldicyandiamide (19·5 g.) and *cyclo*hexylamine (15 g.). The *base* (yield, 12·1 g.) formed colourless plates from benzene, m. p. 172—173° (Found: C, 57·2; H, 6·8; N, 23·45. $C_{14}H_{20}N_5Cl$ requires C, 57·2; H, 6·8; N, 23·85%).

N¹-p-*Chlorophenyl*-N⁵ : N⁵-cyclo*tetramethylenediguanide* (4204).—Prepared as described for 4172 using pyrrolidine (10 c.c.). The *base* formed colourless plates from toluene, m. p. 206 (Found: C, 54·2; H, 5·8; N, 26·1. $C_{13}H_{16}N_5Cl$ requires C, 54·15; H, 6·0; N, 26·3%).

N¹-p-*Chlorophenyl*-N⁵ : N⁵-cyclo*pentamethylenediguanide* (3926).—(*a*) Prepared as described for (X; R = $[CH_2]_2{\cdot}NEt_2$) from *p*-chlorophenyldicyandiamide (9·5 g.) and piperidine (6·4 g.), the mixture being refluxed for 4 hours. The *base* (yield, 2·8 g.) formed colourless needles from xylene, m. p. 190—192° (Found: C, 56·8; H, 6·5; N, 24·65. $C_{13}H_{18}N_5Cl$ requires C, 55·7; H, 6·45; N, 25·0%). (*b*) *p*-Chlorophenyldicyandiamide (3·9 g.), piperidine (3 c.c.), ethanol (40 c.c.), and copper bronze powder (3·8 g.), refluxed for 16 hours, gave a solution of the copper complex which, when worked up in the usual manner, yielded crude base (2·2 g.), and needles (1·1 g.) from xylene identical with material from (*a*). (*c*) *p*-Chlorophenyldicyandiamide (3·9 g.) refluxed for 16 hours in piperidine (5 c.c.) also gave the base (0·2 g.) from xylene, m. p. 185° undepressed in admixture with material from (*a*).

N¹-p-*Chlorophenyl*-N⁵ : N⁵-*anhydrobis-(β-hydroxyethyl)diguanide* (5157).—Prepared as described for (X; R = $[CH_2]_2{\cdot}NEt_2$) from *p*-chlorophenyldicyandiamide (9·7 g.) and morpholine (10 c.c.). The *base* formed colourless needles (yield, 5·6 g.) from toluene, m. p. 188—189° (Found: C, 51·4; H, 5·7; N, 24·15. $C_{12}H_{16}ON_5Cl$ requires C, 51·15; H, 5·65; N, 24·85%). The *acetate*, prepared in acetone, formed colourless needles, m. p. 207—208° (Found: C, 49·35; H, 5·8; N, 20·2. $C_{12}H_{16}ON_5Cl,CH_3{\cdot}CO_2H$ requires C, 49·2; H, 5·85; N, 20·5%).

N¹-p-*Chlorophenyl*-N⁵-*methoxydiguanide* (X; R = OMe) (5234).—Prepared as described for (X; R = Et) from *p*-chlorophenyldicyandiamide (8·3 g.) and methoxylamine hydrochloride (3·8 g.) with an added equivalent of sodium hydroxide, the mixture being refluxed for 10 hours. The *base* (yield, 1·25 g.) formed colourless needles from toluene, m. p. 161—161·5° (Found: C, 45·3; H, 5·15; N, 28·0; Cl, 14·4. $C_9H_{12}ON_5Cl$ requires C, 44·7; H, 5·0; N, 29·0; Cl, 14·7%).

N¹-p-*Chlorophenyl*-N⁵-*methyl*-N⁵-*β-methoxyethyldiguanide* (4171).—Prepared as described for 4172 using β-methoxyethylmethylamine (10 c.c.). The *base* (yield, 2·5 g.) formed colourless needles from aqueous methanol, m. p. 91—93° (Found: C, 50·65; H, 6·1; N, 24·0. $C_{13}H_{18}ON_5Cl$ requires C, 50·7; H, 6·3; N, 24·65%).

N¹-*Phenyl*-N⁵-*methyl*-N⁵-iso*propyldiguanide* (4461).—Prepared as described for 4172 using phenyldicyandiamide (9·0 g.) and methyl*iso*propylamine (13 c.c.), the mixture being refluxed for 1½ hours. The *base*, isolated after decomposition of the copper complex, gave colourless prisms (5·1 g.) from light petroleum (b. p. 100—120°), m. p. 101·5—103° (Found: C, 60·9; H, 7·4; N, 29·65. $C_{12}H_{19}N_5$ requires C, 61·8; H, 8·15; N, 30·0%). The acetate, prepared in acetone, had m. p. 188—191°.

N¹-*Phenyl*-N⁵ : N⁵-*diethyldiguanide* (4210).—Similarly prepared from phenyldicyandiamide (8 g.) and diethylamine (10 c.c.). The *base* formed colourless prisms from light petroleum (b. p. 100—120°), m. p. 100—101° (Found: C, 61·5; H, 7·55; N, 29·25. $C_{12}H_{19}N_5$ requires C, 61·8; H, 8·15; N, 30·0%).

N¹-*Phenyl*-N⁵ : N⁵-*di-n-butyldiguanide* (4492).—Similarly prepared using di-*n*-butylamine (15 c.c.). The crude base was an oil, which was converted into the sparingly soluble solid iodide by adding excess of potassium iodide to a solution of the hydrochloride, and thence into a solution of the base in ether by shaking with dilute sodium hydroxide. The ethereal solution was dried (KOH) and treated with glacial acetic acid (1 c.c.); the acetate then crystallised out as colourless needles, m. p. 139—140° (Found: C, 61·1; H, 8·9; N, 19·7. $C_{16}H_{27}N_5,CH_3{\cdot}CO_2H$ requires C, 61·9; H, 8·9; N, 20·0%).

N¹-p-*Tolyl*-N⁵ : N⁵-*dimethyldiguanide* (4175).—Prepared as described for the *p*-chlorophenyl analogue (4134) using *p*-tolyldicyandiamide (8·7 g.). The base formed colourless plates (4·5 g.), m. p. 149—149·5°, which rapidly absorbed carbon dioxide from the atmosphere and, therefore, by neutralising a solution in excess dilute hydrochloric acid with ammonia, was isolated as the hydrochloride which crystallised from water in colourless needles, m. p. 224—225° (Found: C, 51·95; H, 7·05; N, 26·65. $C_{11}H_{17}N_5,HCl$ requires C, 51·6; H, 7·05; N, 27·4%).

N¹-3′ : 4′-*Xylyl*-N⁵ : N⁵-*diethyldiguanide* (4969).—Prepared, as described for (X; R = Et), using 3 : 4-xylyldicyandiamide (9·4 g.) and diethylamine (5 g.). The *acetate* (3·8 g.), prepared in benzene in place of acetone, had m. p. 182—184° (Found: C, 59·65; H, 7·85; N, 22·0. $C_{14}H_{23}N_5,CH_3{\cdot}CO_2H$ requires C, 59·8; H, 8·4; N, 21·8%), and was converted into the *base*, which formed colourless plates from light petroleum (b. p. 60—80°), m. p. 70—71° (Found: C, 63·8; H, 8·4; N, 26·6. $C_{14}H_{23}N_5$ requires C, 64·4; H, 8·8; N, 26·8%).

N¹-p-*Anisyl*-N⁵ : N⁵-*dimethyldiguanide* (4174).—Prepared as described for the *p*-tolyl analogue 4175 using *p*-anisyldicyandiamide (9·7 g.). The *base* (6·2 g.) formed colourless prisms from toluene, m. p. 142—143° (Found: C, 56·25; H, 7·05; N, 29·35. $C_{11}H_{17}ON_5$ requires C, 56·15; H, 7·2; N, 29·8%).

N¹-p-*Anisyl*-N⁵ : N⁵-*diethyldiguanide* (4125).—Similarly prepared using diethylamine (10 c.c.), the mixture being refluxed overnight. The *base* formed colourless prisms, m. p. 93—94° (Found: C, 58·95; H, 7·45; N, 26·4. $C_{13}H_{21}ON_5$ requires C, 59·3; H, 8·0; N, 26·6%).

N¹-p-*Anisyl*-N⁵ : N⁵-cyclo*pentamethylenediguanide* (3781).—(*a*) Prepared as described for (X; R = $[CH_2]_2{\cdot}NEt_2$) using *p*-anisyl dicyandiamide (9·5 g.) and piperidine (6·4 g.). The *base* formed colourless prisms (4·5 g.) from toluene, m. p. 144—146° (Found: C, 61·2; H, 8·1; N, 25·6. $C_{14}H_{21}ON_5$ requires C, 61·1; H, 7·6; N, 25·4%).

(*b*) *p*-Anisyldicyandiamide (9·5 g.), piperidine (12·7 g.), dioxan (12 c.c.), and 5N-hydrochloric acid (10 c.c.) refluxed for 15 hours gave after crystallisation from toluene a base (2·9 g.) identical with that prepared as in (*a*).

N¹-p-*Nitrophenyl*-N⁵ : N⁵-*diethyldiguanide* (4376).—Prepared as described for 4172 from *p*-nitrophenyldicyandiamide (10 g.) and diethylamine (10 c.c.), the mixture being refluxed for 3 hours, the copper complex digested with the hydrochloric acid at 70° and the *base* isolated and crystallised from aqueous β-ethoxyethanol, from which it separated in yellow leaflets, m. p. 121—122° (Found: N, 20·7. $C_{12}H_{19}O_2N_6$ requires N, 21·0%).

N¹-p-*Acetamidophenyl*-N⁵-*methyl*-N⁵-iso*propyldiguanide* (4566).—Prepared similarly from *p*-acetamidophenyldicyandiamide (19 g.) and methyl*iso*propylamine (20 c.c.), the mixture being refluxed for 1½ hours; the precipitated copper complex was digested with cold 1·5N-hydrochloric acid (700 c.c.) and decomposed by sodium sulphide; the filtrate, made alkaline with sodium hydroxide, saturated with common salt, and kept overnight, deposited the crude base (5 g.) which was converted into the *acetate* in acetone, giving colourless prisms, m. p. 206—208° (Found: C, 54·85; H, 7·15. $C_{14}H_{23}ON_6$ requires C, 54·85; H, 7·4%).

N^1 : N^5-*Diphenyldiguanide* (4202).—Phenyldicyandiamide (5 g.), aniline hydrochloride (6·5 g.), dioxan (25 c.c.), and water (10 c.c.) were refluxed for 2 hours and cooled, and the precipitate was crystallised from water to give colourless needles of the *hydrochloride* (2·2 g.), m. p. 232° (Found: Cl′, 12·2. $C_{14}H_{15}N_5$,HCl requires Cl′, 12·2%). The base, formed by adding sodium hydroxide to a solution in hot water, gave needles from methanol, m. p. 145—146°.

N^1-p-*Chlorophenyl*-N^5-*phenyldiguanide*.—Similarly prepared from *p*-chlorophenyldicyandiamide (19·5 g.) and aniline hydrochloride (26 g.). The *hydrochloride* formed colourless plates from aqueous methanol, m. p. 248° (Found: Cl′, 11·0. $C_{14}H_{14}N_5Cl$,HCl requires Cl′, 10·95%). The base formed colourless plates from aqueous methanol, m. p. 149°.

N^1-p-*Chlorophenyl*-N^5-p-*anisyldiguanide* (4123).—Similarly prepared using *p*-anisidine (24·6 g.), and with addition of 10N-hydrochloric acid (18 c.c.). The initial precipitate, redissolved in boiling 2N-hydrochloric acid (500 c.c.), filtered from solid impurity, and made alkaline with sodium hydroxide, gave the *base*, which formed colourless needles (12·5 g.) from ethanol, m. p. 155° (Found: C, 56·05; H, 4·9; N, 21·8. $C_{15}H_{14}ON_5Cl$ requires C, 56·6; H, 5·0; N, 22·0%).

N^1-p-*Chlorophenyl*-N^5-*β-naphthyldiguanide* (4970).—Similarly prepared using β-naphthylamine (28·6 g.) previously dissolved in hot 2N-hydrochloric acid (90 c.c.), the mixture being refluxed for 6 hours. The crude *hydrochloride* which formed colourless prisms from aqueous β-ethoxyethanol, m. p. 249—250° (Found: C, 57·35; H, 4·2; N, 19·5. $C_{18}H_{16}N_5Cl$,HCl requires C, 57·75; H, 4·5; N, 18·7%), was converted into the crystalline *base*, m. p. 142—143°, by adding 10N-sodium hydroxide (15 c.c.) to a suspension in hot methanol (250 c.c.) (Found: C, 64·1; H, 4·95; N, 19·9. $C_{18}H_{16}N_5Cl$ requires C, 63·9; H, 4·7; N, 20·7%).

N^1 : N^5-*Di*-p-*anisyldiguanide* (4124).—Similarly prepared from *p*-anisyldicyandiamide (9·5 g.) and *p*-anisidine (12·3 g.) dissolved in 5N-hydrochloric acid (20 c.c.). The *hydrochloride* (11 g.) formed colourless prisms from water, m. p. 222° (Found: C, 55·2; H, 5·85; N, 19·85. $C_{16}H_{19}O_2N_5$,HCl requires C, 54·85; H, 5·45; N, 20·0%).

N^1 : N^5-*Di*-p-*tolyldiguanide*.—Similarly prepared from *p*-tolyldicyandiamide (8·7 g.) and *p*-toluidine (10·7 g.) dissolved in 5N-hydrochloric acid (20 c.c.). The *hydrochloride* formed colourless needles from water, m. p. 231—234° (Found: N, 21·7; Cl′, 11·4. $C_{16}H_{19}N_5$,HCl requires N, 22·05; Cl′, 11·2%). The *base* formed colourless plates from ethanol, m. p. 187° (Found: C, 67·75; H, 6·45; N, 24·6. $C_{16}H_{19}N_5$ requires C, 68·3; H, 6·75; N, 24·9%).

N^1-p-*Chlorophenyl*-N^3 : N^3-*dialkylguanidines*.

Methyl sulphate (30 c.c.) was added cautiously to a hot suspension of *N*-*p*-chlorophenylthiourea (55·8 g.) in ethanol (300 c.c.) and the whole was refluxed 4 hours. One-sixth of the total volume of the resultant cooled solution was caused to react with dialkylamines as under.

N^1-p-*Chlorophenyl*-N^3 : N^3-*dimethylguanidine*.—An aliquot part of the alcoholic solution was refluxed for 3 hours with aqueous dimethylamine (25%, 27 c.c.), the ethanol distilled off, and the residual syrup dissolved in water (10 c.c.) and sufficient 10N-hydrochloric acid. The *hydriodide*, precipitated by adding potassium iodide, was recrystallised from water giving 7·7 g., m. p. 155—156° (Found: I′, 33·8. $C_9H_{12}N_3Cl$,HI,$3H_2O$ requires I′, 33·5%).

N^1-p-*Chlorophenyl*-N^3 : N^3-*diethylguanidine* (XIV).—Similarly prepared using diethylamine (11 g.). The *hydriodide* separated from water as colourless needles, m. p. 67—68° (Found: I′, 34·0; after drying in vacuum at 50°. $C_{11}H_{16}N_3Cl$,HI requires I′, 34·1%).

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150. *Enolic Derivatives of 3 : 6-Diketo-Δ⁴-cholestene.*

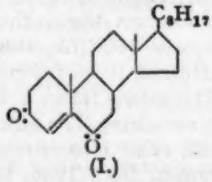
By WALTER C. J. ROSS.

3 : 6-*Dibenzoyloxy*-$\Delta^{2:4:6}$-*cholestatriene* and 3 : 6-*dibenzoyloxy*-$\Delta^{3:5:7}$-*cholestatriene* have been prepared from 3 : 6-diketo-Δ⁴-cholestene, and some of their reactions have been studied. Benzoylation of the enol ether of 3 : 6-diketo-Δ⁴-cholestene affords 3-*benzoyloxy*-6-*ethoxy*-$\Delta^{2:4:6}$-*cholestatriene*.

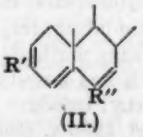
ENOL esters of αβ-unsaturated ketones derived from sterols have been prepared by a number of workers (Heilbron, Kennedy, Spring, and Swain, *J.*, 1938, 869; Ruzicka and Fischer, *Helv. Chim. Acta*, 1936, **19**, 806; Inhoffen, *Ber.*, 1936, **69**, 2141; Westphal, *Ber.*, 1937, **70**, 2126). Westphal has shown that the enol esters derived from Δ⁴-unsaturated 3-ketones have a $\Delta^{3:5}$-unsaturated structure. No enol esters of unsaturated 1 : 4-diketones appear to have been prepared in the sterol field.

It has been shown in these laboratories (unpublished results) that Δ⁴-cholesten-3-one and Δ⁴-androstene-3 : 17-dione readily yield enol benzoates when refluxed for a short time with benzoyl chloride, and it is now found that 3 : 6-diketo-Δ⁴-cholestene (I) affords two different compounds according to the conditions employed.

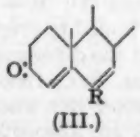
The lower-melting compound, formed in presence of pyridine, is the *dienol dibenzoate* of structure (II; R′ = R″ = OBz), since it can be hydrolysed with hot dilute acid or alkali to give the parent diketone (I). It exhibits an absorption maximum at 3070 A., $\epsilon = 18{,}200$, which is entirely similar to that of *iso*ergostatrienone enol acetate (II; R′ = OAc, R″ = H, and with C_8H_{17} side-chain) which shows a maximum at 3040 A., $\epsilon = 16{,}600$ (Heilbron *et al.*, *loc. cit.*). When a slight excess of alcoholic potassium hydroxide is added to a cold solution of the dibenzoate the optical rotatory power and the light absorption characteristics of the solution change.



(I.)



(II.)



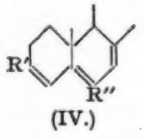
(III.)

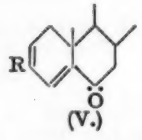
The solution remains laevorotatory, but the numerical value of the rotation falls slightly. The absorption maximum at 3070 A. is replaced by a double maximum at 2800 and 2900 A., $\epsilon = 14{,}500$; during this change an

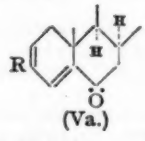
amount of alkali corresponding to the hydrolysis of one benzoate group is consumed. It is suggested that partial hydrolysis occurs with formation of the ester (III; R = OBz); 3-keto-$\Delta^{2:4}$-cholestadiene (III; R = H) exhibits an absorption maximum in the same region (at 2800 A., ϵ = 40,000). Unfortunately, no crystalline material could be isolated from the solution after this mild hydrolysis.

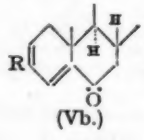
The higher-melting compound, formed with benzoyl chloride alone, is also a *dibenzoate*, as shown by analysis and the consumption of two equivalents of alkali on complete hydrolysis. It is formulated as 3 : 6-dibenzoyloxy-$\Delta^{3:5:7}$-cholestatriene (IV; R′ = R″ = OBz) and this structure is supported by light-absorption measurements. The substance exhibits an absorption maximum at 3160 A., ϵ = 20,200, which is very similar to that of ergostatrienone enol acetate (IV; R′ = OAc, R″ = H, C_9H_{17} side-chain) which shows a maximum at 3165 A., ϵ = 21,400 (Heilbron *et al.*, *loc. cit.*), and that of $\Delta^{3:5:7:22}$-ergostatetrene (IV; R′ = R″ = H, C_9H_{17} side-chain), maximum at 3160 A., ϵ = 19,000 (*idem*, *ibid.*). The triene system in structure (IV) is more heavily substituted than that in structure (II), and as would be expected the absorption maximum for the compound to which structure (IV) has been assigned occurs at a somewhat longer wave-length. As in the case of the dienol benzoates now described, the ergosterol derivative of structure (IV) has a higher melting point (146° as against 137°) than that of structure (II), and also a numerically greater value of the optical rotation (−143·5° as against −84·6°). 3 : 6-Dibenzoyloxy-$\Delta^{3:5:7}$-cholestatriene gives a positive Tortelli–Jaffé reaction as might be expected from the proposed formulation.

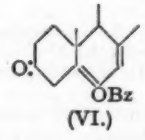
Complete hydrolysis of this dibenzoate with hot alcoholic potassium hydroxide yields a non-crystalline product, $[\alpha]_D^{20°}$ +48°, which exhibits an absorption maximum at 2560 A., ϵ = 3020. The position of this maximum is consistent with the formation of a compound with the grouping O:C·C:C·C:O (cf. I) though the intensity is of a low order [3 : 6-diketo-Δ^4-cholestene (I) shows a maximum at 2520 A., ϵ = 14,400]. The sign of the rotation indicates that the asymmetric centre at C_8 is involved in the hydrolysis mechanism. Treatment of 3 : 6-dibenzoyloxy-$\Delta^{3:5:7}$-cholestatriene with cold alcoholic potassium hydroxide—under conditions which cause complete hydrolysis of cholestenone enol benzoate—produces interesting changes in the optical rotatory power and of the light-absorption characteristics. The optical rotation soon changes from $[\alpha]_D^{20°}$ −85° to a positive value, finally becoming steady at +97°; the absorption maximum moves to 3100 A., ϵ = 7270. During this treatment the solution develops a deep orange colour, which gives rise to a yellow-green fluorescence on acidification with acetic acid. The hydrolysis of this dibenzoate is more difficult to interpret, particularly as no crystalline product was obtainable at either stage. One would expect the 3-benzoate group to be hydrolysed first with the formation of compound (VI): this explanation is, however, improbable since this substance would almost certainly be laevorotatory (compare 7-dehydrocholesterol, $[\alpha]_D^{20°}$ −113°) and would have an absorption maximum at the wave-lengths 2700—2800 A. It is now suggested that hydrolysis occurs at the 6-benzoate group and that it is accompanied by a rearrangement leading to the formation of the monobenzoate (V; R = OBz). In the conversion of structure (IV) into structure (V) two isomers (Va and Vb) could be formed which differ in the mode of locking of rings B and C; the existence of such a mixture could account for the fact that the hydrolysis products of this dibenzoate could not be crystallised.

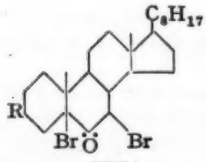

(IV.)

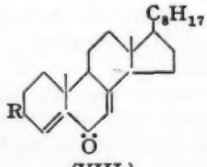

(V.)

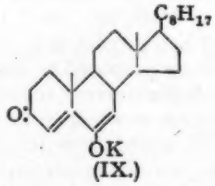

(Va.)

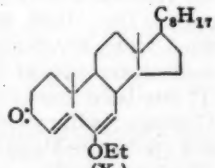

(Vb.)


(VI.)


(VII.)


(VIII.)


(IX.)


(X.)

A somewhat similar change is recorded by Heilbron, Jackson, Jones, and Spring (*J.*, 1938, 102). Debromination of (VII; R = OAc) might be expected to give (VIII; R = OAc), but (V; R = OAc) is actually obtained. In our case hydrolysis of (IV; R′ = R″ = OBz) at the 6-benzoate group would be expected to give (VIII; R = OBz), but we suggest that (V; R = OBz) is actually formed. This structure accounts for the observed absorption maximum and for the sign of the rotation (compare V; R = OAc, Heilbron *et al.*, *loc. cit.*, which has a maximum at 3170 A., ϵ = 6300 and $[\alpha]_D^{20°}$ +27°). Dr. E. R. H. Jones informs the author that 6-keto-$\Delta^{2:4}$-cholestadiene (V; R = H) exhibits an absorption maximum at 3160 A., ϵ = 7500 (unpublished work).

It had been hoped to prepare the mono-enol benzoates, which have been assumed to be intermediate hydrolysis products of the dibenzoates, by the following methods. 3 : 6-Diketo-Δ^4-cholestene forms a potassium compound (Windaus, *Ber.*, 1906, **39**, 2249) which has now been shown to have structure (IX) since it yields the known 6-enol ether (X) when heated with ethyl iodide. The structure of this ether is confirmed by the fact that it exhibits an absorption maximum at 2950 A. (Butenandt and Schramm, *Ber.*, 1936, **69**, 2289); the alternative structure (V; R = OEt) would be expected to show an absorption maximum at a longer wave-length. Treatment of the potassium compound with benzoyl chloride under the appropriate conditions should

give the monobenzoate (III; R = OBz); it has, however, not been found possible to prepare the ester by the methods tried so far. Benzoylation of the enol ether in the presence of pyridine affords the expected *3-benzoyloxy-6-ethoxy-*$\Delta^{2:4:6}$*-cholestatriene* (II; R′ = OBz, R″ = OEt), m. p. 126—127°, $[\alpha]_D^{20°}$ −48°, which exhibits an absorption maximum at 3080 A., ϵ = 13,200. This compound is re-converted into the enol ether on treatment with cold sodium methoxide. Mild acid hydrolysis of the compound would be expected to give the monobenzoate (V; R = OBz)—compare the conversion of testosterone enol ether into testosterone (Serini and Koster, *Ber.*, **1938**, **71**, 1769). In practice, it has not been found possible to de-ethylate the compound without simultaneous elimination of the benzoate group.

When kept in solution 3 : 6-dibenzoyloxy-$\Delta^{2:5:7}$-cholestatriene undergoes interesting changes which can be followed by observing the optical rotation. The change in optical rotatory power is similar to that observed on partial hydrolysis; indeed, a very similar yellow-green fluorescence develops in the neutral or faintly acid solutions, and benzoic acid is liberated. As crystalline products could not be obtained in either case, it has not been possible to confirm the identity of the end produets. The rotation change is considerably accelerated by exposure to light, is relatively unaffected by traces of acid, and is definitely retarded by a small amount of alkali.

Experimental.

M. ps. were determined in sealed capillaries and are uncorrected; unless otherwise stated light-absorption measurements were made in chloroform–alcohol (1 : 1) solution; rotations were determined in chloroform solution.

Difficulty has been experienced in the preparation of Δ⁴-cholestene-3 : 6-dione by direct oxidation of cholesterol. The yields obtained by the methods described in the literature have been uniformly low. The oxidation of cholesterol by chromic acid in acetic acid solution has been studied and the following method has been found to give consistent results. Advantage has been taken of the fact that the diketone can be extracted from ether solution by concentrated alkali (Windaus, *loc. cit.*) to develop an improved method of isolating the substance from the oxidation mixture.

Cholesterol (100 g.) was dissolved in warm acetic acid (4 l.) and the solution was cooled to 25° with vigorous stirring; this gave a fine suspension of crystals. A mixture of chromic acid (50 g.), water (50 c.c.), and acetic acid (500 c.c.) was added during ½ hour with stirring. The temperature during the addition was maintained at 23—25° by cooling. The mixture was next stirred for 2 hours at 20°, by which time the separated cholesterol had passed back into solution. After being diluted with six times its volume of water, the mixture was extracted with ether (total, 2 l.). The extract was washed twice with dilute sulphuric acid, once with water, and then with sufficient 10N-sodium hydroxide to render the mixture almost neutral. The aqueous layer was then run off and the ether layer was well shaken with excess of 10N-sodium hydroxide which extracted the acidic material and the diketone, a deep yellow sludge being formed. The supernatant ethereal layer was poured off and the aqueous layer was washed with fresh ether; it was then diluted with ten times its volume of water and re-extracted with ether. The dried ethereal layer gave a solid product (30 g.) on evaporation; this, after recrystallisation from methanol, had m. p. 122—123°. A twice recrystallised specimen had m. p. 124—125°, $[\alpha]_D^{20°}$ −38° (c = 0·54).

If the temperature is kept below 20° during the addition of the oxidising mixture a 5—10% yield of cholestane-3 : 6-dione-5-ol is obtained while the yield of the above diketone falls to 10—15%. The former compound can easily be separated from the mixture because of its relative insolubility—it remains suspended in the initial ether extract and can be filtered off. It has been converted into the unsaturated diketone by heating for a short time just above the m. p. or by heating with potassium hydrogen sulphate, but a more convenient method is to suspend it in twenty times its volume of benzene and to reflux the mixture with excess of phosphoric oxide for ½ hour. The benzene solution is then percolated through a short column of alumina in order to remove any unchanged material: the evaporated eluate gives the required diketone, m. p. 122°.

3 : 6-*Diketo-*Δ⁴*-cholestene-6-enol Ether.*—A solution of the potassium compound of 3 : 6-diketo-Δ⁴-cholestene was prepared by adding the theoretical amount of N/10-alcoholic potassium hydroxide to a hot solution of the compound in ten times its volume of alcohol. The solution became deep green and appeared red by transmitted light. Excess of ethyl iodide was added and the mixture was refluxed until it was neutral to moist litmus paper. During this heating the solution first changed to a light orange and then to an intense crimson colour. On dilution with water a red gum separated; this solidified on rubbing with methanol. After one crystallisation from methanol, followed by a washing with light petroleum (which removed most of the adsorbed red colour), the product had m. p. 161—163°. A mixture with a specimen, m. p. 166°, prepared according to the directions of Windaus (*Ber.*, 1907, **40**, 257) had m. p. 162—164°. A purified specimen of the ether made by Windaus's method had $[\alpha]_D^{20°}$ +2°. It gives a yellow coloration with a solution of antimony trichloride in chloroform.

3-Benzoyloxy-6-ethoxy-$\Delta^{2:4:6}$*-cholestatriene.*—The enol ether (1 g.) was refluxed for 20 minutes with a mixture of pyridine (5 c.c.) and benzoyl chloride (5 c.c.). The product was poured into a large excess of water and agitated until the benzoyl chloride had been hydrolysed. The water was then poured off the gum and methanol was added; in a short time the mass had become solid, and the mixture was then boiled and cooled, and the solid filtered off. The product was dissolved in ether and methanol was added; on boiling off the ether the *compound* separated in small prisms (0·8 g.), m. p. 126—127°, $[\alpha]_D^{20°}$ −48° (c = 0·80) (Found: C, 81·1; H, 9·4. $C_{36}H_{50}O_3$ requires C, 81·5; H, 9·5%). Light absorption: maximum at 3080 A., ϵ = 13,200. The substance gives a yellow coloration with a solution of antimony trichloride in chloroform; a yellow-orange colour in the Liebermann–Burchard test; and a faint yellow coloration when its solution in chloroform–alcohol is treated with one drop of 10N-sodium hydroxide.

Hydrolysis of the above Ester.—The ester (100 mg.) was shaken overnight with sodium methoxide (10 c.c., 3%) in methyl alcohol. The mixture deposited fine prismatic needles, m. p. 162—163°, not depressed by admixture with the enol ether of 3 : 6-diketo-Δ⁴-cholestene.

3 : 6-*Dibenzoyloxy-*$\Delta^{2:4:6}$*-cholestatriene.*—3 : 6-Diketo-Δ⁴-cholestene (2 g.) was heated under reflux for ½ hour with pyridine (10 c.c.) and benzoyl chloride (10 c.c.). The product was worked up as before and the dibenzoate was recrystallised from ether–methanol, also as described above. The yield of *dibenzoate*, m. p. 178—179°, was 1·75 g. After a chromatographic purification by percolating a solution in benzene through a column of activated alumina and evaporating the colourless eluate the substance crystallised from ether–methanol in flattened needles, m. p. 179—180°, $[\alpha]_D^{20°}$ −32° (c = 0·80) (Found: C, 81·5, 80·9; H, 8·4, 8·5. $C_{41}H_{50}O_4$ requires C, 81·2; H, 8·3%). Light absorption: maximum at 3070 A., ϵ = 18,200. The substance gives an eosin-like coloration with a solution of antimony trichloride in chloroform; a pale green colour in the Liebermann–Burchard test; a yellow coloration when its solution in chloroform–alcohol is treated with one drop of 10N-sodium hydroxide; and a negative Tortelli–Jaffé reaction.

3 : 6-*Dibenzoyloxy-*$\Delta^{2:5:7}$*-cholestatriene.*—3 : 6-Diketo-Δ⁴-cholestene (3 g.) was heated under reflux for ½ hour with

benzoyl chloride (10 c.c.). Most of the excess of benzoyl chloride was removed by distillation at 1—2 mm.; the *product* then partly solidified. The crude material was ground under light petroleum (b. p. 40—60°) and the solid (1·5 g.) was filtered off and washed with cold acetone. After a chromatographic purification as above, it crystallised from acetone in colourless flattened needles, m. p. 205—208°, $[\alpha]_D^{20°}$ −85° (c = 1·15) (Found : C, 80·8, 80·9; H, 8·2, 8·0. $C_{41}H_{60}O_4$ requires C, 81·2; H, 8·3%). Light absorption : maximum at 3160 A., ϵ = 20,200; maximum at 3160 A., ϵ = 18,800 (in *cyclo*hexane solution). The substance gives an intense eosin-like coloration with a chloroform solution of antimony trichloride; the following rapidly changing sequence of colours in the Liebermann–Burchard test: pink with yellow fluorescence, green with yellow fluorescence, deep green, deep blue; a deep orange coloration when its solution in chloroform–alcohol is treated with one drop of 10N-sodium hydroxide; and a positive reaction (brown-green layer at the interface) in the Tortelli–Jaffé test.

Hydrolysis of 3 : 6-Dibenzoyloxy-$\Delta^{2:4:6}$-cholestatriene.—(1) The dibenzoate (200 mg.) was heated under reflux with N/10-alcoholic potassium hydroxide (10 c.c.) for one hour : titration of the excess of alkali indicated that 6·7 c.c. had been used (theory for the complete hydrolysis of two benzoate groups is 6·6 c.c.). The mixture was then heated to boiling and diluted with water until a permanent precipitate formed. This was quickly filtered off and the filtrate was re-heated and allowed to cool slowly. Large plates were deposited and these after recrystallisation from methanol had m. p. 122—123°, unaltered by admixture with an authentic specimen of 3 : 6-diketo-Δ^4-cholestene.

(2) The dibenzoate (200 mg.) was dissolved in chloroform (12·5 c.c.) and N/10-alcoholic potassium hydroxide (7·5 c.c.) was added. Finally the volume of the solution was made up to 25 c.c. with alcohol and the mixture was left at room temperature. The rotation which originally corresponded to $[\alpha]_D^{20°}$ −32° became −16° after 24 hours and had not changed further after 48 hours (both these values being calculated on the weight of dibenzoate used). A solution similarly treated showed the following light absorption changes :

Hours after addition of alkali.	Maxima at		Intensity ϵ =	
0	2300 A.	3070 A.	48,400	18,200
2	2300 A.	2800—2900 A.	35,000	15,100
20	2300 A.	2800—2900 A.	34,000	14,500

The absorption maximum at 2300 A. is due to the benzoyl groups; the intensity of this maximum falls because potassium benzoate slowly crystallises from the solution. No other crystalline material could be isolated from the mixture.

Hydrolysis of 3 : 6-Dibenzoyloxy-$\Delta^{3:5:7}$-cholestatriene.—(1) The ester (200 mg.) was hydrolysed as described above; 6·0 c.c. of alkali were consumed. The product, which could not be crystallised even after a chromatographic resolution, had $[\alpha]_D^{20°}$ +48° (c = 0·80) and exhibited an absorption maximum at 2560 A., ϵ = 3020. The ester was recovered unchanged after heating with excess of sodium carbonate or bicarbonate, or after heating with an alcoholic solution of hydrogen chloride for one hour.

(2) When the ester was treated with alcoholic potassium hydroxide in the cold under the conditions described above the rotation changed from −85° to +97°. The solution had to be acidified with acetic acid before the rotation was taken since it had become of such a deep red colour that it was opaque to sodium light. After acidification it showed a yellow-green fluorescence. The absorption spectrum changes during this alkali treatment were as follows :

Hours after addition of alkali.	Maximum at		Intensity ϵ =	
0	2300 A.	3160 A.	37,600	20,200
2	2300 A.	3100 A.	34,600	9,700
20	2300 A.	3100 A.	34,600	7,270
After acidification	2300 A.	3080 A.	34,600	7,270

Once again no crystalline material could be isolated despite repeated attempts.

Rotation Changes in Solutions of the Dibenzoates.—A solution of the dibenzoate (II; R′ = R″ = OBz), m. p. 179—180°, appeared to undergo no change of rotatory power on keeping in light, but when a solution of the higher-melting isomeride (IV) was exposed to diffused daylight in a stoppered flask the following changes were observed (all values are calculated on the weight of dibenzoate taken). The solution which was in B.P. chloroform had c = 0·76.

Time (hours)	0	17	41	65	89	233	329	377	425
$[\alpha]_D^{20°}$	−83°	−57°	−26°	−3°	+16°	+64°	+92°	+102°	+103°

Assuming that the change from $[\alpha]_D^{20°}$ −83 to +103° represents the complete action, the following table shows the amount of action after 100 hours under varying conditions. In each experiment 25 c.c. of solution (c = 1·0 in B.P. chloroform) were used.

Conditions.	% Action in 100 hours.
Kept in darkness in neutral solution	7·5
Kept in diffused daylight in neutral solution	46·5
Kept in diffused daylight with 2 drops of acetic acid added	48·5
Kept in diffused daylight with 2 drops of N/10-hydrochloric acid added	53·5
Kept in diffused daylight with 2 drops N/10-sodium hydroxide added	27·0

The action is accompanied by hydrolysis since benzoic acid can be extracted from the solution by shaking with a little sodium carbonate solution. During the above changes the solution assumes a yellow-green fluorescence.

The author's thanks are due to Professor G. A. R. Kon for his interest in this work, to Dr. E. A. Braude for measuring the absorption spectra, and to Organon Laboratories, Ltd., for permission to publish the results.

RESEARCH DEPARTMENT, ORGANON LABORATORIES, LTD., LONDON, W.C.2. [*Received, February 11th,* 1946.]

151. *Experiments on the Interaction of Hydroxy-compounds and Phosphorus and Thionyl Halides in the Absence and in the Presence of Tertiary Bases. Part V.*

By W. Gerrard.

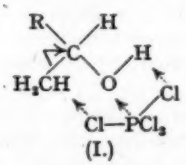
(+)Octan-2-ol and phosphorus pentachloride in the presence of respectively ether and carbon disulphide yielded rapidly at −10° (−)2-chloro-octane and octylene; but the pentabromide under the same conditions afforded phosphoric esters as well as the (−)bromide. It is evident that there is a primary action of the pentahalide and a secondary action of the resulting oxyhalide, the latter action being in certain circumstances ineffective. The function of pyridine chiefly concerns the secondary action of the oxyhalide, which in the presence of sufficient alcohol produces phosphoric ester.

(−)Phenylmethylcarbinol and the pentahalides under conditions described above rapidly gave rise to the (+)halides in large yield but with considerable loss in rotatory power, and thus afforded examples of the reaction represented closely by $PX_5 + ROH = RX + POX_3 + HX$. Pyridine appeared to have little influence on the primary action of the pentahalide; but in the presence of sufficient alcohol the secondary action of the oxyhalide gave rise to (+)halide, RX, having a high rotatory power.

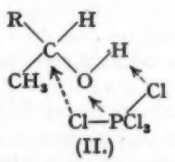
Probable mechanisms in terms of end-on and broadside collisions are suggested.

Although the interaction of hydroxy-compounds and phosphorus pentachloride has been represented by the equation, $ROH + PCl_5 = POCl_3 + RCl + HCl$, in the majority of papers referring to this reaction (cf. Clark and Streight, *Proc. Roy. Soc. Canada*, **1929**, **23**, 77) the yields of chloride, RCl, were stated as small or not stated at all. Pierre and Puchot (*Annalen*, **1872**, **163**, 253), using the pentachloride (1 mol.), obtained *n*-propyl chloride (29% yield) from the alcohol (4 mols.), and *n*-butyl chloride (31% yield) from the alcohol (5 mols.). It was pointed out (Part II, *J.*, 1945, 106) that the oxychloride may react on its own account and have a considerable influence on the nature and yields of products. The significance of order and speed of mixing will depend on the relative velocities of the primary (PCl_5) and subsequent ($POCl_3$) reactions at the prevailing temperature.

(+)Octan-2-ol interacted slowly with the oxychloride (Part II, *loc. cit.*) at 15° and formed (−)2-chloro-octane, and the esters, $POCl_2OR$, $POCl(OR)_2$, $PO(OR)_3$, in proportions depending on relative amounts of reagents. It is now shown that (+)octan-2-ol (1 mol.) and the pentachloride (1 mol.) interacted very quickly at −10° without the intervention of the oxychloride; but instead of the expected theoretical yield of the chloride, RCl (1 mol.), (−)2-chloro-octane was produced in yield approaching only 50%, the other product noticed being octylene. There was no sign of the formation of phosphoric esters. It is suggested that the chloride, RCl, was produced by the end-on mechanism, $Cl_4PCl \dashrightarrow R{-}OH \longrightarrow ClR + Cl_4P^{+} + \bar{O}H \longrightarrow ClR + Cl_4POH \longrightarrow ClR + POCl_3 + HCl$; whilst a broadside elimination mechanism (I) would account for the formation of octylene. This elimination mechanism is pictured as being due to a type of hyperconjugation.



(I.)



(II.)

As compared with the oxychloride, the greater ease of reaction of the pentachloride may be attributed to three factors. First, since in most compounds phosphorus is 4-covalent, this number being exceeded only with the halogens, it is to be expected that phosphorus in the 5-covalent state will show a decided tendency to resume the 4-covalent state. Secondly, the trigonal bipyramidal structure of the pentachloride (cf. Mills, *J.*, 1942, 457) appears to confer a high probability of effective orientation on collision. Thirdly, the co-ordinately linked oxygen may be expected to reduce the activity of the chlorine atoms in the oxychloride.

Essentially similar results had previously been obtained by Houssa and Phillips (*J.*, 1932, 108), but it is now shown that, as the reagents were then mixed and refluxed in boiling ether, the temperature was far beyond the minimum requirements of the pentachloride. The two experiments are complementary, however, and show that the production of octylene was not related to the temperature prevailing, and even at the higher temperature phosphorus oxychloride did not intervene. It is evident that a structural factor is concerned in the probability of such intervention. In an exploratory experiment it was found that 1·8 mols. of *n*-butyl alcohol were required to cause the disappearance of the pentachloride (1 mol.) suspended in ether at −10°, and considerable amounts of phosphoric esters were produced.

Addition of (+)octan-2-ol (1 mol.) to the pentabromide (1 mol.) suspended in ether (or dissolved in carbon disulphide) at −10° led to the rapid formation of (−)2-bromo-octane (52%) and phosphoric esters.

The function of pyridine depends on the relative proportions of the reagents as well as on conditions. Addition of (+)octan-2-ol (1 mol.) and pyridine (1 mol.) to the pentachloride (1 mol.) in carbon disulphide at −10° caused the immediate formation of (−)2-chloro-octane in yield approximately the same as, and octylene in much less yield than, when the pyridine was omitted. Pyridine hydrochloride and phosphoric esters were also formed. The base appeared to have little influence on the end-on attack of the pentachloride, but it did facilitate the broadside attack of the oxychloride during the mixing, and so gave rise to phosphoric

esters. Addition of the pentachloride (0·25 mol.) to (+)octan-2-ol (1 mol.) and pyridine (1 mol.) in carbon disulphide solution led to the rapid formation of (−)2-chloro-octane in considerably diminished yield (based on the amount of alcohol), and to the much slower formation of phosphoric ester by the broadside attack of the oxychloride facilitated most probably by the hydrogen bonded base, ROH . . . . NC_5H_5. Analogous results were obtained when phosphorus pentabromide was used, except that the oxybromide appeared to be more effective in the formation of phosphoric ester.

Hückel and Pietrzok (*Annalen*, 1939, **540**, 250) used pyridine (4 mols.) for each mol. of *l*-menthol and pentachloride in petroleum, and they suggested mechanisms based on the prior formation of ions of the type $(C_5H_5N:PCl_4)^{+}\,Cl^{-}$, $(R-\overset{H}{O}:P(Cl_4):NC_5H_5)^{+}$ the former leading to the reaction: $Cl^{-} \longrightarrow ROH = RCl + OH^{-}$.

Whereas McKenzie and Clough (*J.*, 1913, **103**, 687) obtained only a viscid oil containing phosphorus by the interaction of the pentachloride and phenylmethylcarbinol under unspecified conditions, Kenyon, Phillips, and Taylor (*J.*, 1931, 382) obtained the (+)chloride, RCl, (with considerable loss in rotatory power) in 53·5% yield by the addition of the (−)alcohol (1 mol.) to ice cold pentachloride (2 mols.) followed by heating on a steam-bath. They obtained the *dl*-chloride, RCl, in 87·5% yield by the addition of an ethereal solution of the *dl*-alcohol to a boiling solution of the pentachloride (2 mols.). It is now shown that the interaction of the (−)alcohol (1 mol.) and respectively the pentachloride and the pentabromide (1 mol.) suspended in ether or dissolved in carbon disulphide is rapid at −10°. Yields of (+)halides, RX, were large, especially for the bromide, but there was still considerable loss in rotatory power. All the phosphorus was found in the aqueous washings; and as it has been shown (Part II, *loc. cit.*) that the interaction of this alcohol and phosphorus oxychloride is slow at 0°, it may be concluded that the equation, $ROH + PX_5 = RX + POX_3 + HX$, closely represents the reaction. The author suggests that the end-on mechanism accounted for the inversion and a broadside one (II) for the retention of configuration. The elimination mechanism (I) noticed with octan-2-ol was evidently by-passed, because the electron-releasing function of the phenyl group would compensate any electron demand of the reactive carbon atom more readily than would the hyperconjugation mechanism. There was no sign of the intermediate chlorophosphate in these experiments.

Holmberg (*Ber.*, 1912, **45**, 997) used the pentabromide in ethereal solution and obtained 1-bromo-1-phenylethane, $\alpha_D^{14°}$ +1·5° (from ROH, $\alpha_D^{17°}$ −4·4°).

The function of pyridine appears to be twofold. The only influence it appears to have on the primary interaction of the pentahalide is to precipitate the hydrogen halide as C_5H_5NHX, and thus to prevent any direct action of this gas. In the experiment of Kenyon, Phillips, and Taylor (*loc. cit.*) (cf. present expt. 10) 1-chloro-1-phenylethane (70%), $[\alpha]_{5461}$ + 10·4°, was obtained by the addition of the alcohol, $[\alpha]_{5461}$ −49·8°, (1 mol.) and pyridine (1 mol.) to the pentachloride (2 mols.) at 0° followed by 30 minutes' heating at 50°. It is highly probable that, so far as the direct attack of the pentachloride was concerned, the reaction took place during the actual mixing at 0°, and the rather higher rotatory power of the chloride was due to the suppression of the incidental interaction of the hydrogen chloride and alcohol, $PCl_5 + ROH + C_5H_5N = POCl_3 + RCl + C_5H_5N,HCl$. A secondary influence of the base is more fundamental and concerns the subsequent interaction of the oxyhalide and alcohol when the proportions are suitably adjusted. It was shown in Part II (*loc. cit.*) that addition of oxychloride to a mixture of (−)phenylmethylcarbinol, $\alpha_D^{18°}$ (l = 10 cm.) −25·6°, and pyridine in ethereal solution at 0° caused production of (+)1-chloro-1-phenylethane, $\alpha_D^{18°}$ (l = 10 cm.) + 63·0°, from the beginning, and the precipitate had a composition represented by $C_5H_5N,HCl,C_5H_5NPO_2Cl$. Closely similar results have now been obtained with the reagents in carbon disulphide. It is quite clear that the configuration retention mechanism tends to be completely eliminated, probably by the end-on mechanisms suggested in Part II. Now when the pentachloride (0·5 mol.) in carbon disulphide was added at −10° to a solution of (−)alcohol (1 mol.) and pyridine (2 mols.) there appeared to be a rapid formation of some (+)chloride, RCl, (with some loss in rotatory power) by the primary interaction of the pentachloride, followed on standing by a slower secondary interaction of the oxychloride and alcohol, which in the presence of free base yielded the (+)chloride, RCl, having a high rotatory power. The net result was the isolation of (+)chloride, RCl, having $\alpha_D^{16°}$ (l = 10 cm.) + 78·1°, and a precipitate which appeared to have the composition $xC_5H_5N,HCl + yC_5H_5NPO_2Cl$, where in contrast with the composition stated above, x is appreciably greater than y. Analogous results were obtained with the pentabromide, (−)alcohol, $\alpha_D^{16°}$ (l = 10 cm.) − 14·8°, yielding the (+)bromide, RBr, having $\alpha_D^{14°}$ (l = 10 cm.) + 31·1°.

Loss of Rotatory Power in Substitution Reactions.—In the systems under consideration there are probably three distinct causes of partial loss in rotatory power. The most probable, in the author's opinion, is the occurrence of end-on inversion mechanisms together with broadside retention mechanisms, the former usually occurring more readily, and therefore preponderant inversion is commonly observed. A second is the occurrence of successive substitutions, $\overset{-}{X} \longrightarrow R\text{------}\overset{-}{X}$ (Hughes, Juliusburger, Masterman, Topley, and Weiss, *J.*, 1935, 1525), and a third is the symmetrical addition to a planar carbonium cation (Cowdrey, Hughes, Ingold, Masterman, and Scott, *J.*, 1937, 1196, 1201, 1208, 1236, 1243, 1252; cf. McKenzie and Gow, *J.*, 1933, 705).

The difference in behaviour of phenylmethylcarbinol and octan-2-ol has been of considerable interest, and in the light of the herein reported rotatory power of (+)1-chloro-1-phenylethane, $[\alpha]_D^{18°}$ +93·5°, a brief statement on the position is desirable. Thionyl chloride alone and (−)phenylmethylcarbinol afforded (−)1-chloro-1-phenylethane, $[\alpha]_D^{20°}$ −50·6° (McKenzie and Clough, *loc. cit.*), and the postulated mechanism to account for

retention of configuration is the intramolecular decomposition of the intermediate chlorosulphinate facilitated by the electron-releasing function of the phenyl group (Kenyon and Phillips; Ingold and Hughes). It now appears that the inversion mechanism must have operated to a significant extent. With phosphorus trichloride the (−)carbinol yielded the (+)chloride, $[\alpha]_D^{18°}$ +8·1° (McKenzie and Clough) (cf. Part I), indicating only a small preponderance of inversion over retention mechanism.

The high rotatory power reported herein gives added significance to the doubts expressed by Ingold and Hughes concerning the optical purity of the specimens of the methyl and the ethyl ether of phenylmethylcarbinol used as reference material. It follows that some extension of the correlation of steric course and the S_Ni mechanism may be necessary to include examples in which no loss of rotatory power is shown. The preparation of 1-bromo-1-phenylethane having $\alpha_D^{18°}$ (l = 10 cm.) + 131·4° has an interesting bearing on the experiments of Levene and Rothen (*J. Biol. Chem.*, 1939, **127**, 237; cf. Arcus, *J.*, 1944, 236). The flattening of the molecular rotation curve for the bromide, RBr, prepared at temperatures approaching −80° has been taken as indicating a maximum rotatory power of $[M]_{5780}$ 90°, in benzene. This value, however, is only half the molecular rotation, in benzene, of the bromide, RBr, having $\alpha_D^{18°}$ (l = 10 cm.) 131·4°.

Experimental.

General Procedures.—In the absence of pyridine, the alcohol, dissolved in dry ether or dry carbon disulphide, was mixed dropwise at −10° with the phosphorus pentahalide, suspended in ether or dissolved in carbon disulphide. A filtering flask fitted with a tap funnel was used, and the side tube was attached to a U tube containing pellets of potassium hydroxide to absorb any hydrogen halide evolved. Unless otherwise stated, ice was added immediately after completion of mixing (15 mins.), and the organic solution was washed with a dilute solution of sodium carbonate, dried quickly with potassium carbonate, and left over sodium sulphate. Phosphate and halide ions were determined quantitatively in the aqueous washings, and the contents of the absorption tube were examined for halide ions.

In the presence of pyridine, the precipitate, which formed during or subsequently to the mixing, was separated by rapid filtration, and kept in a vacuum desiccator for 1 hour before being weighed and analysed. The filtrate was treated as already described except that a washing with a dilute solution of sulphuric acid preceded that with sodium carbonate, and pyridine was determined quantitatively in the aqueous washings.

After removal of the solvent, the residue was distilled.

Rotatory powers are recorded for l = 10 cm.

Interaction of (−)Phenylmethylcarbinol and Phosphorus Pentahalides.—Expt. 1. At the end of the dropwise addition of an ethereal solution (10 c.c.) of the carbinol ($\alpha_D^{18°}$ −14·8°; 2·44 g.; 1 mol.) to the pentachloride (4·17 g.; 1 mol.) covered with dry ether (10 c.c.), the solid had just disappeared. Ice was added immediately. (+)1-Chloro-1-phenylethane (2·5 g., 89%), b. p. 64—65°/9 mm., $\alpha_D^{14°}$ +4·0°, was obtained, and there was only a trace of residue. The absorption tube contained a trace of chloride ion. The aqueous washings contained almost all the phosphorus in the system (Found: P, 0·618 g. Calc.: P, 0·620 g.) and 4/5ths of the chlorine in the system (Found: Cl, 2·82 g.).

Expt. 2. The same quantities of reagents in carbon disulphide solution (50 c.c.) afforded (+)1-chloro-1-phenylethane (2·21 g., 80%), b. p. 73°/13 mm., $\alpha_D^{16°}$ +9·4° (Found: Cl, 25·2. Calc.: Cl, 25·2%), and the remaining data were essentially the same.

Expt. 3. The same carbinol (2·44 g.; 1 mol.) in ethereal solution (10 c.c.) was added to phosphorus pentabromide (8·60 g., 1 mol.) covered with ether (10 c.c.) at −10° (15 mins.); by the end of this operation the pentabromide had disappeared. Ice was immediately added. By distilling the ethereal solution, (+)1-bromo-1-phenylethane (2·90 g.; 79%), b. p. 85·5°/9 mm., $\alpha_D^{14°}$ +11·8° (Found: Br, 43·0. Calc.: Br, 43·2%), and a residue (0·6 g.) were obtained. The absorption tube contained only a trace of bromide ion; all the phosphorus and 4/5 of the bromine in the system were found in the aqueous washings.

Expt. 4. When the reagents were used in carbon disulphide, the bromide, RBr, (93%), had b. p. 89°/14 mm., $\alpha_D^{16°}$ +9·4° (Found: Br, 43·5%), the remaining data being essentially the same.

Expt. 5. The pentachloride (2·6 g.; 0·5 mol.) dissolved in carbon disulphide (50 c.c.) was added at −10° to a solution of (−)carbinol ($\alpha_D^{18°}$ −44·0°; 3·05 g.; 1 mol.) and pyridine (4·0 g.; 2 mols.) in the same solvent (10 c.c.). Formation of a white solid commenced immediately, and proceeded slowly at −10°. After the mixing was complete (15 mins.) the mixture was kept at 15° for 12 hours. From the filtered solution, (+)1-chloro-1-phenylethane (1·86 g.; 53%) b. p. 69°/11 mm., $\alpha_D^{18°}$ +78·1° (Found: Cl, 25·0%), and a residue (decomp.) (0·65 g.) were obtained. The white solid (5·43 g.) dissolved slowly but completely in water (Found: Cl, 28·3; P, 6·6; C_5H_5N, 54·8%), and was probably a mixture of rather more than one mol. of pyridine hydrochloride and less than one of the compound $C_5H_5NPO_2Cl$, together with a small amount of quaternary compound, C_5H_5NRHX, where X is an acid radical. Nearly all the phosphorus in the system was found in the solid (0·360 g. compared with 0·387 g.); the remainder was in the aqueous washings. Of the 4 g. of pyridine used, 2·98 g. were found in the solid, and 0·760 g. in the aqueous washings; the difference, 0·26 g., had probably gone to form the quaternary compound the presence of which was demonstrated by the precipitation of the ferrocyanide (Gerrard *J.*, 1936, 688).

Expt. 6. Repetition of expt. 5, except that 8 g. of pyridine (4 mols.) were used, led to the formation of a white solid (6·20 g.) (Found: Cl, 25·9; P, 6·1; C_5H_5N, 53·8%), (+)1-chloro-1-phenylethane (2·0 g.; 57%), b. p. 71·5°/13 mm., $\alpha_D^{16°}$ +83·4° (Found: Cl, 25·2%), and a residue (0·4 g.). Since the aqueous washings contained 4·18 g. of pyridine, it follows that again rather less than 2 mols. of pyridine have reacted for each mol. of carbinol. Details of results are similar to those recorded for expt. 5.

Expt. 7. The quantities specified in expt. 6, but with the pentachloride suspended in ether, gave rise to (+)chloride, RCl, (2·0 g.), b. p. 68°/10 mm., $\alpha_D^{16°}$ +66·1°, and a solid (5·69 g.) (Found: Cl, 28·8; P, 6·7; C_5H_5N, 48·4%). More than half the pyridine in the system (4 mols.) was found in the aqueous washings. Again nearly all the phosphorus was in the solid.

Expt. 8. The pentabromide (3·5 g.; 0·4 mol.) was added slowly to an ethereal solution (20 c.c.) of the alcohol ($\alpha_D^{18°}$ −14·8°; 2·44 g.; 1 mol.) and pyridine (4·8 g.; 3 mols.) at −10°. Precipitation of solid proceeded slowly, and particles of the pentabromide persisted in suspension for some time, even when the mixture was removed from the cooling bath and occasionally shaken for 3 hours at 15°. After being at 15° for 12 hours the mixture was filtered. The solid (5·554 g.) [Found: Br, 41·8; P, (as PO_4), 2·8; C_5H_5N, 42·9%] contained half the pyridine in the system. The aqueous washings contained only a trace of phosphate ion (Found: Br′ ≡10·1 c.c. of 0·1N-$AgNO_3$; C_5H_5N, 2·13 g.). From the ethereal solution, (+)1-bromo-1-phenylethane (1·52 g., 41%), b. p. 84°/9 mm., α_D^{14} + 31·1° (Found: Br, 43·4. Calc.: Br, 43·2), and a residue, which decomposed at the end of the distillation, were obtained.

Expt. 9. With the same reagents dissolved in carbon disulphide, precipitation of solid (4·910 g.) (Found: Br, 38·7;

P, 3·3; C_5H_5N, 49·7%) proceeded slowly, but much more quickly than in expt. 8. Aqueous washings contained traces of bromide and phosphate ions and 2·27 g. of pyridine, *i.e.*, 1·5 mols. of base had reacted. 1-Bromo-1-phenylethane (1·95 g.), b. p. 84—85°/9 mm., $\alpha_D^{14°}$ +30·1° (Found, Br, 43·3%), was obtained.

Expt. 10. (+)1-Chloro-1-phenylethane (1·90 g., 68%), b. p. 70—71°/12 mm., $\alpha_D^{16°}$ +12·4° (Found : Cl, 25·1%), and a decomposed residue (0·55 g.) were obtained by the addition (15 mins.) of the pentachloride (4·2 g.; 1 mol.) to the alcohol ($\alpha_D^{14°}$ − 16·0°; 2·44 g.; 1 mol.) and pyridine (1·6 g.; 1 mol.) in carbon disulphide at −10°, followed by immediate filtration and work-up. The precipitate (3·20 g.) (Found : Cl, 40·7; P, 6·7; C_5H_5N, 48·1%) appeared to be a mixture of pyridine hydrochloride and possibly the substance, $PCl_4ONHC_5H_5$.

Interaction of (+)*Octan-2-ol* ($\alpha_D^{18°}$ +8·0°) *and Phosphorus Pentahalides.*—*Expt.* 1. At the end of the addition (15 mins.) of (+)octan-2-ol (3·25 g.; 1 mol.) in ether (10 c.c.) to the pentachloride (5·21 g.; 1 mol.) suspended in ether (10 c.c.) at −10°, the solid had just disappeared. Ice was immediately added. Octylene and (−)2-chloro-octane (1·80 g.; 48%), b. p. 63°/15 mm., $\alpha_D^{16°}$ −29·8° (Found : Cl, 23·8. Calc. : Cl, 23·9%), but no residue, were obtained. The aqueous washings contained : P, 0·725 g.; Cl′, 3·62 g. (System contained : Cl, 4·44 g.; P, 0·775 g.). No oil was formed when the carbonate washings were acidified. During the addition, no hydrogen chloride passed into the absorption tube; and even when, during the following 15 mins., dry hydrogen was passed through the solution at −10°, an insignificant amount of hydrogen chloride (equivalent to 3·4 c.c. of 0·1N-$AgNO_3$) was collected. When the solution was allowed to warm to 15° (15 mins.) and then agitated by a stream of hydrogen, the amount of hydrogen chloride evolved in 15 mins. was equivalent to 25·6 c.c. of 0·1N-$AgNO_3$.

Expt. 2. By the same procedure, but with carbon disulphide (50 c.c.) as solvent, octylene, (−)2-chloro-octane (1·81 g.), b. p. 63°/15 mm., $\alpha_D^{16°}$ −29·0°, but no residue, were obtained. During the mixing and subsequent passage of hydrogen (15 mins.) at −10°, hydrogen chloride (0·805 g.) was evolved. The aqueous washings contained : Cl′, 2·862 g.; P, 0·722 g.

Expt. 3. The alcohol (2·6 g.; 1 mol.) was added to a suspension of pentabromide (8·6 g.; 1 mol.) in ether (20 c.c.) at −10°. A little pentabromide remained unreacted at the end of the addition (15 mins.). Ice was immediately added. From the ethereal solution, (−)2-bromo-octane (2·0 g.; 52%), b. p. 69°/8 mm., $\alpha_D^{16°}$ −34·9° (Found : Br, 41·8. Calc. : Br, 41·45%), a fraction, b. p. 90—105°/8 mm. (0·43 g.), and a residue (0·33 g.) (Found : P, 4·6%) were obtained. No hydrogen bromide was evolved during the mixing, a little (equiv. to 2·8 c.c. of 0·1N-$AgNO_3$) was carried off in a stream of hydrogen (15 mins.) at −10°, and rather more (equiv. to 18·1 c.c. of 0·1N-$AgNO_3$) at 15° (15 mins.). The aqueous washings contained : Br, 6·04 g.; P (as PO_4), 0·49 g. (in system, Br, 8·00 g.; P, 0·620 g.), and the carbonate extract afforded a trace of oil.

Expt. 4. Essentially the same results were obtained when carbon disulphide was used in place of ether. No hydrogen bromide was evolved at −10°, and in a stream of hydrogen at −10° some of the former gas (equiv. to 19·1 c.c. of 0·1N-$AgNO_3$) was carried away in 15 mins.

Expt. 5. The pentachloride (2·09 g.; 0·25 mol.) in carbon disulphide (30 c.c.) was added to the alcohol (5·2 g.; 1 mol.) and pyridine (3·2 g., 1 mol.) in the same solvent (10 c.c.) at −10°. Precipitation of pyridine hydrochloride began immediately, but was far from complete at the end of the addition, and after being at 15° for 48 hours the mixture was filtered. The solid (4·10 g. Calc. for C_5H_5NHCl, 1 mol. : 4·62 g.) (Found : Cl, 32·1; C_5H_5N, 65·9. Calc. : Cl, 30·7; C_5H_5N, 68·4%) was pyridine hydrochloride contaminated by a substance, possibly $C_5H_5NHOPCl_4$. The aqueous washings of the carbon disulphide solution contained only traces of chloride and phosphate ions. From the solvent, (−)2-chloro-octane (0·90 g.), b. p. 63—64°/15 mm., $\alpha_D^{16°}$ −20·9°, the alcohol, b. p. 78—80°/10 mm. (0·65 g.), and a residue (oil-bath at 140°) (2·5 g.) (Found : P, 7·2. Calc. for $OP(OR)_3$: P, 7·1%) were obtained. The carbonate extract yielded a trace of oil.

Expt. 6. The pentabromide (4·31 g.; 0·25 mol.) in carbon disulphide solution (30 c.c.) was added to the alcohol (5·2 g.; 1 mol.) and pyridine (3·2 g.; 1 mol.) in the same solvent (20 c.c.) at −10°. Precipitation of the hydrobromide of the base commenced immediately but continued subsequently at 15° (48 hours). The solid (6·44 g. Calc. : 6·4 g.) (Found : Br, 49·0; C_5H_5N, 49·2. Calc. : Br, 50·0; C_5H_5N, 49·4%) was separated, and from the carbon disulphide solution (−)2-bromo-octane (1·20 g.), b. p. 69°/9 mm., $\alpha_D^{16°}$ −28·1° (Found : Br, 41·6%), and a residue (3·81 g.) (oil-bath 140°) (Found : P, 7·0%) were obtained. Aqueous washings contained only traces of bromide and phosphate ions.

Addition (15 mins.) of a solution of the alcohol (4·4 g.; 1 mol.) and pyridine (2·7 g.; 1 mol.) in carbon disulphide to the pentachloride (7 g.; 1 mol.) in the same solvent at −10° caused the immediate precipitation of a white solid (4·622 g.) (Found : Cl, 42·7; P, 3·1; C_5H_5N, 51·4%). Phosphorus pentabromide behaved analogously.

Houssa and Phillips (*loc. cit.*) added an ethereal solution of the alcohol [$\alpha_{5461}^{20°}$ +9·62° (l = 1·0); 1 mol.] and pyridine (2 mols.) to the pentachloride (1 mol.) and then heated the mixture for 30 mins. An unspecified amount of 2-chloro-octane, $\alpha_{5461}^{23°}$ −34·86° (l = 1·0), and considerable amounts of phosphoric esters were obtained.

Rotatory Powers of 1-*Halogeno*-1-*phenylethanes.*—In repetition of an experiment described in Part II (*loc. cit.*) but with carbon disulphide instead of ether as solvent, phenylmethylcarbinol ($\alpha_D^{16°}$ −44·0°; 3·66 g.; 1 mol.), pyridine (4·8 g.; 2 mols.), and phosphorus oxychloride (3·07 g.; 0·67 mol.) were used. The white precipitate (7·24 g.) (Found : Cl, 19·1; P, 7·9; C_5H_5N, 45·7%) closely resembled that (7·38 g.) (Found : Cl, 19·2; P, 7·9; C_5H_5N, 46·3%) previously described, and the other product isolated was (+)1-chloro-1-phenylethane, b. p. 72·5°/12 mm., $\alpha_D^{16°}$ −99·6° (Found : C, 68·6; H, 6·6; Cl, 25·1. Calc. : C, 68·3; H, 6·4; Cl, 25·2%).

By repeating expt. 5, Table IV, Part III (*J.*, 1945, 848), but with carbon disulphide as solvent, 1-bromo-1-phenylethane, b. p. 83°/9 mm., $\alpha_D^{18°}$ +131·4° (from ROH, $\alpha_D^{16°}$ −44·0°) (Found : C, 52·1; H, 5·1; Br, 43·1. Calc. : C, 51·9; H, 4·9; Br, 43·2%), was obtained.

Rotatory Power of 2-*Bromo-octane.*—Repetitions of expt. 6, Table I, Part III (*loc. cit.*), but with hydrogen instead of carbon dioxide to agitate the liquid, led to uniform results : 2-bromo-octane, b. p. 70·5°/10 mm., $\alpha_D^{18°}$ −42·6° (from ROH, $\alpha_D^{16°}$ +7·92°) (Found : C, 50·0; H, 8·8; Br, 41·2. Calc. : C, 49·7; H, 8·8; Br, 41·45%), was obtained.

Phenylmethylcarbinol was resolved by the procedure of Downer and Kenyon (*J.*, 1939, 1156), octan-2-ol by that of Kenyon (*J.*, 1922, **121**, 2540).

The author records his thanks to Dr. R. W. West for helpful discussions.

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152. *An Interpretation of the Sandmeyer Reaction. Part VIII. The Decomposition of Diazonium Salts by Cupric Chloride in Neutral and Acid Solution.*

By Herbert H. Hodgson.

Cupric chloride is an effective catalyst for the replacement of the diazo-nitrogen of strongly positive diazonium kations by chlorine in both weakly acid and neutral solutions, but much less efficient for weak kations; it is superior to cuprous chloride under the above conditions. The negative ($-I$) inductive effect of the methoxyl group strongly influences the decomposition of diazotised *o*- and *p*-anisidine. The results are held to support the complex anion theory.

In Part VI of this series (Hodgson and Sibbald, *J.*, 1945, 545) it was recorded that a neutral solution of *p*-nitrobenzenediazonium chloride when treated with hydrated cupric chloride afforded an 85% yield of *p*-chloronitrobenzene, a result which appeared to indicate that substitution of the diazonium group by chlorine had occurred *via* the mechanism of a complex hydrated cupric chloride anion (cf. Harker, *Z. Krist.*, 1936, **93**, 136; Chrobak, *ibid.*, 1934, **88**, 20; Hendricks and Dickinson, *J. Amer. Chem. Soc.*, 1927, **49**, 2149). A similar mechanism had been suggested previously for the parallel experiment in hydrochloric acid solution (Hodgson and Sibbald, Part V, *J.*, 1944, 393). It consequently appeared of interest to examine whether this reaction of cupric chloride was a general one for aryl diazonium chlorides, and the table below contains the data of a representative set of such reactions, all carried out under identical conditions.

From the table it will be seen that for amines which give highly positive diazonium kations, such as the nitroanilines and *p*-chloroaniline, cupric chloride is an effective catalyst for the replacement of the diazonium group by chlorine under both acidic and neutral conditions. For amines, however, whose diazonium kations are much less positive, such as those from aniline, the three toluidines, and α- and β-naphthylamine, cupric chloride is practically ineffective. Benzidine gives a slightly improved yield compared with the last named amines, but in 3 : 3′-dichlorobenzidine, where the chlorine atoms greatly increase the positivity of the diazonium kation by the negative ($-I$) effect, the amount of replacement by chlorine is considerably improved. Anthranilic acid, however, gives mainly salicylic acid both in acid and neutral decompositions. At the slight acidities of the acid reactions, the catalytic power of the cupric chloride is generally somewhat inferior to that in neutral solutions. In solutions of the less positive diazonium kations the main reaction is phenol formation, and the phenol in neutral solution tends to couple with undecomposed diazo-compound, a reaction which is very pronounced in the benzidine decompositions. When the neutral decompositions were carried out with calcium carbonate also present, little or no steam-volatile product was obtained, owing to azo-dye formation.

With *m*- and *p*-nitrobenzenediazonium chlorides, cuprous chloride gives smaller yields than cupric chloride under both acid and neutral conditions, thereby confirming the result of Part V (*loc. cit.*).

Neutral solutions of *o*- and *p*-nitrobenzenediazonium chlorides saturated with sodium chloride gave no chloronitrobenzene and *m*-nitrobenzenediazonium chloride gave only 6% of *m*-chloronitrobenzene, whereas when hydrochloric acid was present small yields of the chloronitro-compounds were obtained in all three reactions (cf. Hodgson and Birtwell, Part I, *J.*, 1941, 770, who postulate un-ionised hydrogen chloride as the main active reagent and not the chloride ion; cf. also Hodgson and Sibbald, Part VI, *loc. cit.*).

In the decompositions of diazotised *o*- and *p*-anisidines there is a surprisingly large replacement of the diazonium group by chlorine, indicating that the negative ($-I$) inductive effect of the methoxyl group is predominant and has appreciably increased the positivity of the diazonium group.

Previous work by Contardi (*Ann. Chim. Appl.*, 1923, **7**, 13) in fairly strong acid solution had shown that the substitution of the amino-group by chlorine (or bromine), particularly in amines with strong electro-negative substituents ortho or para to the amino-group, was readily attained by allowing cupric chloride (or bromide) to react with the respective diazonium salt [cf. Hodgson, *J. Soc. Dyers and Col.*, 1926, **42**, 365, who found that a mixture of copper sulphate and sodium chloride (or bromide) was also effective]. Contardi believed that the replacement proceeded through an undefined complex salt to which Hodgson and Birtwell (*loc. cit.*) (cf. also Hodgson and Sibbald, *J.*, 1945, 819) gave a more precise form.

Experimental.

General Procedure.—A solution of the amine (g.-mol./50) in a mixture of hydrochloric acid (10 c.c., *d* 1·18) and water (30 c.c.), was diazotised by the addition at 0° (floating ice) of sodium nitrite (2 g.) dissolved in a little water; *o*- and *p*-nitroanilines, however, were diazotised as usual. Excess of nitrous acid was removed by urea, and the solution either (*a*) filtered and treated with hydrated cupric chloride (7 g.), or (*b*) neutralised with calcium carbonate, filtered, and then treated with the cupric chloride (7 g.). It was then diluted so that the total volume of water used was 100 c.c., saturated with sodium chloride, kept at room temperature for 30 minutes, and finally heated gradually to the boil before steam distillation, which was carried out at such a dilution that solid salt was always present. The steam distillate containing the volatile chloro-compound was treated with sodium hydroxide (10 g.) if the phenolic product also formed was steam-volatile, and again steam distilled. Solid products were weighed and identified; liquid products were extracted with ether, the extract dried, the ether removed, and the residue weighed and identified.

Table of Decomposition Data.

Amine diazotised.	Chloro-compound obtained.	Yield (%). (*a*) Acid.	(*b*) Neutral.	Blank. (*a*).	(*b*).	Other data.
Aniline	Chlorobenzene	18	18	9	9	
o-Toluidine	*o*-Chlorotoluene	15	15	15	1·5	(*b*) 56% *o*-Cresol.
m-Toluidine	*m*-Chlorotoluene	7	7	—	—	(*b*) 54% *m*-Cresol.
p-Toluidine	*p*-Chlorotoluene	22	15	—	—	(*b*) 34% *p*-Cresol.
o-Anisidine	*o*-Chloroanisole	70	75	—	—	Very little hydroxy-compound.
p-Anisidine	*p*-Chloroanisole	67	77	—	—	,, ,, ,,
o-Nitroaniline	*o*-Chloronitrobenzene	85	85	13	0	Practically no *o*-nitrophenol formed.
m-Nitroaniline (cupric chloride)	*m*-Chloronitrobenzene	86	77	13	6	
m-Nitroaniline (cuprous chloride)	*m*-Chloronitrobenzene	75	48	—	—	
p-Nitroaniline (cupric chloride)	*p*-Chloronitrobenzene	75	85	3·5	0	
p-Nitroaniline (cuprous chloride)	*p*-Chloronitrobenzene	60	44	—	—	
Anthranilic acid	*o*-Chlorobenzoic acid with salicylic acid	24 56	27 63	— —	— —	Determined as *p*-nitrobenzene-azosalicylic acid.
p-Chloroaniline	*p*-Dichlorobenzene	30	67	—	—	
α-Naphthylamine	α-Chloronaphthalene	18	22	—	—	
β-Naphthylamine	β-Chloronaphthalene	24	28	—	—	
Benzidine	4 : 4′-Dichlorodiphenyl	22	17	—	—	
3 : 3′-Dichlorobenzidine	3 : 3′ : 4 : 4′-Tetrachloro-diphenyl	48	41	—	—	

The author is indebted to Imperial Chemical Industries Limited (Dyestuffs Division) for gifts of chemicals.

TECHNICAL COLLEGE, HUDDERSFIELD. [*Received, February 23rd,* 1946.]

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153. *Action of Diazomethane on Hydroxy-compounds and of Diazomethane Derivatives on Phenanthraquinone.*

By ALEXANDER SCHÖNBERG and AHMED MUSTAFA.

Certain hydroxy-compounds are stable towards *ethereal* diazomethane solutions, but are readily methylated if methyl alcohol is added. This stability of *o*-hydroxy-ketones is explained by chelation (I). The effect of methyl alcohol is ascribed to its opening of the chelate ring system (VI), thus rendering the *o*-hydroxy-group free. Furthermore, it is believed that diazomethane reacts with the lower alcohols to give the powerful methylating agent $CH_2{:}N{\cdot}NH{\cdot}OR$ or $CH_2{\cdot}N{:}N{\cdot}OR$.

By treatment of 4 : 4′-dihydroxy-αβ-diethylstilbene (stilboestrol) with ethereal diazomethane solution in the presence of *n*-propyl alcohol, its di-*n*-propyl ether was obtained.

1-Benzoyl-2-naphthol (IV) and 6-hydroxy*meso*benzanthrone (V) react with ethereal diazomethane solutions, probably owing to lack of chelation in these substances.

The action of diphenyl-, phenylmethyl-, and phenyl-diazomethane on phenanthraquinone yields methylene-dioxy-derivatives of type (VIII) which give phenanthraquinone when treated with sulphuric acid.

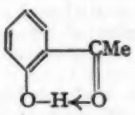
Chrysoquinone reacts in a similar manner (cf. X).

IT has been pointed out that certain *o*-hydroxy-compounds are not methylated by an ethereal solution of diazomethane, *e.g.*, alizarin 2-methyl ether (Herzig and Klimosch, *Monatsh.*, 1909, **30**, 535), the benzopyrone derivative (II) (Shah, Virkar, and Venkataraman, *J. Indian Chem. Soc.*, 1942, **19**, 135), *o*-hydroxyacetophenone (Schönberg and Ismail, *J.*, 1944, 367), and 9 : 10-dihydroxynaphthacene-11 : 12-quinone (Schönberg and Moubasher, *J.*, 1944, 336). This stability is also shown by *o*-hydroxybenzophenone, 1-hydroxy-, 1 : 5-dihydroxy-, and 1 : 4-dihydroxy-anthraquinone, and by the 4-methyl ether of resacetophenone. On the other hand, we find that 1-benzoyl-2-naphthol (IV) and 6-hydroxy*meso*benzanthrone (V) react readily with diazomethane in ethereal solution.

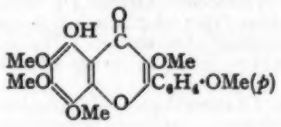
The generally accepted reason (*e.g.*, Sidgwick and Callow, *J.*, 1924, **125**, 527; Perkin and Storey, *J.*, 1928, 233) for the stability of *o*-hydroxy-ketones and related substances towards diazomethane is the formation of a chelated ring system (*e. g.*, I), so the different behaviour of 1-benzoyl-2-naphthol may be ascribed to the large contribution to its resonance structure made by (IV). This *o*-quinonoid structure hinders the formation of a chelated ring, as there is no double bond between C_1 and C_2 (fixation of double bonds), and is in agreement with the yellow colour of the substance. A similar explanation accounts for the methylation of 6-hydroxy*meso*-benzanthrone (V) by diazomethane in ethereal solution.

In agreement with the theory of chelation is the fact that *p*-hydroxyacetophenone and *p* : *p*′-dihydroxy-benzophenone react with ethereal diazomethane, in contrast to *o*-hydroxy-acetophenone and -benzophenone; also 2-hydroxy-1-methylanthraquinone reacts with ethereal diazomethane in spite of the fact that the hydroxy-group is sterically hindered.

Action of Diazomethane in the Presence of Methyl Alcohol.—We have found that *o*-hydroxy-aceto- and -benzo-phenone, the 4-methyl ether of resacetophenone, 1 : 5-dihydroxyanthraquinone, and alizarin 2-methyl



(I.)



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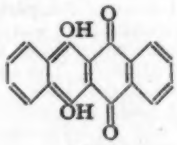

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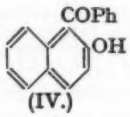

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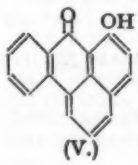

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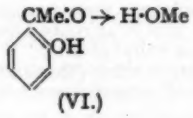

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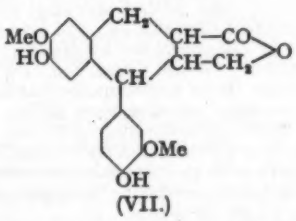


(VII.)

ether, which are stable towards diazomethane in ether, are methylated if methyl alcohol is added to the solution. Further, under the latter conditions, methyl salicylate, conidendrin (VII), and benzophenone oxime are methylated, whereas they are unaffected by ethereal diazomethane (Hölljes and Wagner, *J. Org. Chem.*, 1944, **9**, 40; Brauns, *ibid.*, 1945, **10**, 216; Forster and Dunn, *J.*, 1909, **95**, 425, respectively).

To explain this difference of reactivity caused by the presence of methyl alcohol, it might be assumed that the alcohol reacts with the carbonyl group of the substances concerned to form complexes of the type (VI), in which the phenolic hydroxy-group is free and therefore capable of reacting with diazomethane; but such a theory cannot explain why benzophenone oxime and conidendrin (VII) exhibit this phenomenon or why stilboestrol is only slowly methylated by ethereal diazomethane, but more quickly in the presence of methyl alcohol. The following theory covers the whole field.

It is possible that in methyl-alcoholic solution diazomethane coexists with a compound formed as in (A) (R = Me), which acts as a strong methylating agent. Similarly, for other alcoholic solutions, the corresponding

$$CH_2N_2 + R{\cdot}OH \longrightarrow CH_2{:}N{\cdot}NH{\cdot}OR \text{ or } CH_3{\cdot}N{:}N{\cdot}OR \quad (A)$$

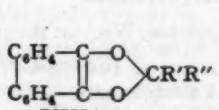
$$CH_3{\cdot}N{:}N{\cdot}OR + Ar{\cdot}OH \longrightarrow Ar{\cdot}OR + CH_2{\cdot}N{:}N{\cdot}OH \longrightarrow N_2 + CH_3{\cdot}OH \quad (B).$$

alkyl group R should be introduced (B). This is indeed the case, for when stilboestrol, dissolved in ether and *n*-propyl alcohol, was treated with ethereal diazomethane, a product was obtained which yielded, after recrystallisation, the pure di-*n*-propyl ether of stilboestrol. The formation of this ether cannot be explained by assuming that the dimethyl ether is first formed by diazomethane and that the two methyl groups are replaced by two *n*-propyl groups by the action of *n*-propyl alcohol, for we found that both stilboestrol and its dimethyl ether are stable towards cold *n*-propyl alcohol.

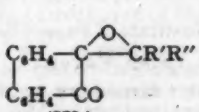
The schemes (A) and (B) account for the production of diazomethane from nitrosomethylurethane and sodium methoxide in the presence of methyl alcohol, rather than sodium ethoxide in the presence of ethyl alcohol, during methylation of phenols by diazomethane. Since, in the latter case, there is the possibility of the formation of the ethyl ether of the phenol in addition to the methyl ether, it is difficult to separate the ethers.

Action of Diazomethane Derivatives on Phenanthraquinone.—We have investigated the action of diphenyl-, phenylmethyl-, and phenyl-diazomethane on phenanthraquinone. *Methylenedioxy*-derivatives (VIII) were obtained as already described in the case of phenanthraquinone and diazomethane (Arndt, Amende, and Ender, *Monatsh.*, 1932, **59**, 202). It is clear that the products obtained by the action of these diazomethanes are not ethylene oxides (IX), for they are easily hydrolysed to phenanthraquinone by concentrated sulphuric acid at room temperature. Under these conditions, a scission of a C–C link is not probable. A methylenedioxy-derivative has also been obtained by the action of diphenyldiazomethane on 6-bromo-1 : 2-naphthaquinone (Fieser and Hartwell, *J. Amer. Chem. Soc.*, 1935, **57**, 1479).

Diazomethane and diphenyldiazomethane converted chrysoquinone into the corresponding *methylene ethers* of 1 : 2-dihydroxychrysene (X; R = R′ = H and R = R′ = Ph, respectively).



(VIII.)



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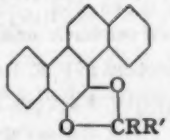

(X.)

Experimental.

The ethereal diazomethane solution was prepared according to *Org. Synth.*, **15**, 3.

Action of Ethereal Diazomethane on p-*Hydroxyacetophenone*,* p : p'-*Dihydroxybenzophenone*,* 2-*Hydroxy*-1-*methylanthraquinone*,* 1-*Benzoyl*-2-*naphthol*,* 6-*Hydroxy*mesobenzanthrone,† 4-*Benzoyl*-1-*naphthol, and* p : p'-*Dihydroxystilbene*.—The hydroxy-compound (1 g.) was dissolved in ether (25 c.c.), the solution cooled in ice, and treated with a cooled ethereal solution of diazomethane (from 4 g. of nitrosomethylurethane). The solvent was evaporated off, and the residue crystallised from alcohol. The resulting methyl or dimethyl ether was identified by m. p. and mixed m. p. with an authentic specimen in each case.

Hydroxy-compounds Unaffected by Ethereal Diazomethane.—Ethereal solutions of 1 g. each of 1-hydroxyanthraquinone,* 1 : 4- and 1 : 5-dihydroxyanthraquinone,* *o*-hydroxybenzophenone,* and resacetophenone 4-methyl ether were treated separately with excess of ethereal diazomethane (from nitrosomethylurethane, 8 g.) as above. The mixtures were left for 48 hours at 0°, and the ether then evaporated, but in every case unchanged starting material was obtained. We confirmed that methyl salicylate (Hölljes and Wagner, *loc. cit.*), benzophenone oxime (Forster and Dunn, *loc. cit.*), and conidendrin (Brauns, *loc. cit.*) also do not react with ethereal diazomethane.

Action of Diazomethane on Hydroxy-compounds in the Presence of Methyl Alcohol.—(*a*) Resacetophenone 4-methyl ether (Adams, *J. Amer. Chem. Soc.*, 1919, **41**, 260) (1 g.) in cold methyl alcohol (about 20 c.c.) was treated with ethereal diazomethane (from nitrosomethylurethane, 8 g.) and the mixture left at 0° for 4 days, during which fresh amounts of the diazomethane solution were added. The solvents were evaporated off, and the oily residue treated with aqueous-alcoholic hydroxylamine hydrochloride. After 4 days at room temperature the mixture was poured into ice-water, and the resulting solid collected and crystallised from ethyl alcohol; it formed colourless crystals, m. p. 127°, not depressed in admixture with resacetophenone oxime dimethyl ether (Sachs and Herold, *Ber.*, 1907, **40**, 2724).

(*b*) Similarly, *o*-methoxybenzophenone was obtained from *o*-hydroxybenzophenone and characterised (m. p. and mixed m. p.) as its oxime.

(*c*) By the same means, alizarin afforded its dimethyl ether (m. p. and mixed m. p.); this was completely insoluble in aqueous sodium hydroxide, whereas in the absence of methyl alcohol the product formed from alizarin was completely soluble in 10% sodium hydroxide, showing that no dimethyl ether was formed.

(*d*) Ethereal diazomethane in the presence of methyl alcohol dimethylated 1 : 5-dihydroxyanthraquinone and converted benzophenone oxime into its *N*-methyl ether and methyl salicylate into its *O*-methyl ether (identified as *o*-methoxybenzoic acid).

(*e*) A suspension of conidendrin (VII) in ether–methyl alcohol was similarly converted by ethereal diazomethane into its dimethyl ether (m. p. not depressed by sample prepared by means of methyl sulphate) (Found : C, 68·3; H, 6·2. Calc. for $C_{22}H_{24}O_6$: C, 68·8; H, 6·2%).

Methylation of 4 : 4'-*Dihydroxy*-α*β*-*diethylstilbene* (*Stilboestrol*).—Stilboestrol (0·4 g.), dissolved in dry ether, was treated with an ethereal solution of diazomethane (from 4 g. of nitrosomethylurethane) and kept at 0° for 24 hours. The product was the dimethyl ether (about 0·1 g.); m. p. not depressed on admixture with an authentic specimen (Reid and Wilson, *J. Amer. Chem. Soc.*, 1942, **64**, 1625). When the above experiment was repeated in the presence of methyl alcohol (10 c.c.) the same ether (0·35 g.) was obtained.

n-*Propylation of Stilboestrol*.—Stilboestrol (0·5 g.) was dissolved in a mixture of ether (25 c.c.) and *n*-propyl alcohol (10 c.c.) and the ice-cooled mixture treated with ethereal diazomethane (from nitrosomethylurethane, 8 g.) added in two portions during 48 hours at 0°. The solvents were evaporated off, the residue was dissolved in ether, and the solution extracted with aqueous potassium hydroxide, washed with water, and dried (sodium sulphate). The ether was driven off, and the residue crystallised from ligroin (b. p. 50—60°); m. p. 98°, not depressed by admixture with an authentic specimen of stilboestrol di-*n*-propyl ether (Reid and Wilson, *loc. cit.*) (Found : C, 81·9; H, 9·0. Calc. for $C_{24}H_{32}O_2$: C, 81·8; H, 9·1%).

Action of Diazomethane Derivatives on Phenanthraquinone.—(a) *Diphenyldiazomethane*. Phenanthraquinone (0·5 g.), suspended in benzene (20 c.c.), was treated with diphenyldiazomethane (Staudinger and Gaule, *Ber.*, 1916, **49**, 1897) (prepared from benzophenone hydrazone, 1·2 g., and yellow mercuric oxide, 3 g.). The quinone dissolved, and after 24 hours at room temperature, the benzene was evaporated off; the oily residue solidified on washing with cold ethyl alcohol, and crystallised from hot absolute ethyl alcohol in almost colourless crystals, m. p. 166—167° (orange melt). The 9 : 10-(*diphenylmethylenedioxy*)*phenanthrene* (VIII; R' = R'' = Ph) dissolves readily in cold benzene or hot ethyl alcohol and with difficulty in light petroleum (b. p. 30—50°). When treated with concentrated sulphuric acid it gives a brownish-violet colour, changing after some time into greenish-brown (Found : C, 86·3; H, 5·1. $C_{27}H_{18}O_2$ requires C, 86·6; H, 4·8%).

(b) *Phenyldiazomethane*. 9 : 10-(*Benzylidenedioxy*)*phenanthrene* (VIII; R = H, R'' = Ph) was obtained by the action of phenyldiazomethane (Staudinger and Gaule, *loc. cit.*) on phenanthraquinone. It formed almost colourless crystals, m. p. 121° (orange melt), soluble in benzene, difficultly soluble in light petroleum (b. p. 30—50°), and dissolving in concentrated sulphuric acid to give a green coloration (Found : C, 83·8; H, 4·8. $C_{21}H_{14}O_2$ requires C, 84·6; H, 4·7%).

(c) *Phenylmethyldiazomethane*. 9 : 10-(α-*Phenylethylidenedioxy*)*phenanthrene* (VIII; R' = Ph, R'' = Me) was similarly obtained by the action of phenylmethyldiazomethane (Staudinger and Gaule, *loc. cit.*); it crystallised in almost colourless crystals from hot ethyl alcohol, m. p. 90° (orange melt), was soluble in benzene, difficultly soluble in light petroleum (b. p. 30—50°), and gave a violet colour with concentrated sulphuric acid (Found : C, 84·3; H, 5·2. $C_{22}H_{16}O_2$ requires C, 84·6; H, 5·1%).

Action of Sulphuric Acid on the Foregoing Three Compounds.—0·5 G. of each of the three methylenedioxyphenanthrenes was mixed with concentrated sulphuric acid (3 c.c.) at room temperature and set aside overnight, during which a green solution was formed. The solution was poured on ice, neutralised with sodium carbonate, and extracted with ether. The ethereal solution was dried (sodium sulphate) and distilled, affording phenanthraquinone (m. p. and mixed m. p.).

Action of Diazomethane Derivatives on 1 : 2-*Chrysoquinone*.—(*a*) Diphenyldiazomethane, under the above conditions, afforded 1 : 2-(*diphenylmethylenedioxy*)*chrysene* (X; R = R' = Ph), colourless crystals, m. p. 264—265° (red melt) (Found : C, 87·2; H, 4·7. $C_{31}H_{20}O_2$ requires C, 87·7; H, 4·7%), from benzene. (*b*) Excess of ethereal diazomethane was added to a suspension of chrysoquinone in ether, and the mixture kept overnight in the ice-chest. The resulting 1 : 2-*methylenedioxychrysene* separated from benzene–ligroin (b. p. 50—60°) in almost colourless crystals, m. p. 158° (Found : C, 83·3; H, 4·8. $C_{19}H_{12}O_2$ requires C, 83·8; H, 4·4%), giving a reddish-brown colour in sulphuric acid. In both cases the action of sulphuric acid, as in the preceding section, regenerated chrysoquinone.

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* These experiments were carried out by Mrs. Abdel Fattah Ismail.

† This experiment was carried out by Miss Wafia Asker.

154. *Attempted Preparation of a Hydroxylated Provitamin-D.*

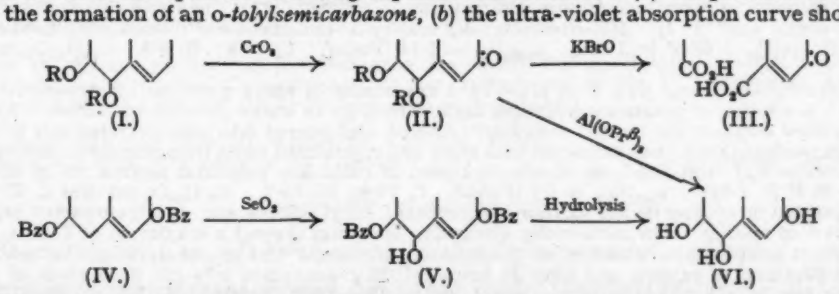
By V. A. Petrow and W. W. Starling.

It was intended to prepare $\Delta^{5:7}$-cholestadien-3(β) : 4(β)-diol, a potential hydroxylated provitamin-D, in order to study the effect of nuclear substitution on the biological activity of the irradiated product. With this aim in view 3(β) : 4(β)-dibenzoyloxy-Δ^5-cholestene (I; R = Bz) has been oxidised with chromic acid to 3(β) : 4(β)-*dibenzoyloxy*-Δ^5-*cholesten*-7-*one* (II; R = Bz). The constitution of the unsaturated 7-keto-diol (II; R = H), obtained on hydrolysis, is established by its conversion into 7-keto- Diels's acid (III). Reduction with aluminium *iso*propoxide gave mainly the dextro-rotatory "α"-Δ^5-*cholesten*-3(β) : 4(β) : 7-*triol* * (VI) together with a small quantity of its C_7 epimeride, the lævo-rotatory "β"-*triol*. The dextro-rotatory "α"-Δ^5-cholesten-3(β) : 4(β) : 7-triol (VI) has been shown to belong to the same stereochemical series in respect of the C_7 hydroxyl-grouping as the dextro-rotatory "α"-Δ^5-cholesten-3(β) : 7-diol, since the dibenzoate (IV) of the latter compound afforded (VI) on selenium dioxide oxidation and subsequent hydrolysis. Attempts to prepare $\Delta^{5:7}$-cholestadien-3(β) : 4(β)-diol by pyrolytic cleavage of the C_7 hydroxyl grouping employing the *tribenzoates* of the two isomerides were not successful.

The only steroid nucleus which has so far been shown to undergo transformation into the vitamin-D type of structure under the action of ultra-violet light is that present in $\Delta^{5:7}$-cholestadien-3(β)-ol (7-dehydrocholesterol). Structural changes in the side chain, such as the presence of an additional methyl grouping (*i.e.*, 22-dihydroergosterol), or of a double bond in the latter (*i.e.*, ergosterol), do not affect the potential activation of these compounds by irradiation. But very slight changes in the positions of the nuclear double bonds apparently prevent activation. Thus $\Delta^{4:6}$-cholestadien-3(β)-ol was prepared by Petrow (*J.*, 1940, 66) for study as a possible precursor of vitamin-D_3, but no evidence of biological activity was detected on irradiation. $\Delta^{6:8}$-Cholestadien-3(β)-ol, a by-product formed during the thermal decomposition of "α"-3 : 7-dibenzoyloxy-Δ^5-cholestene * (Windaus, Linsert, and Eckhardt, *Annalen*, 1938, **534**, 22), was shown by Windaus and Zühlsdorff (*ibid.*, 1938, **536**, 204) to undergo a stereochemical transformation into $\Delta^{6:8}$-coprostadien-3(β)-ol under the action of ultra-violet light. A change in the configuration of the hydroxyl-grouping at C_3, on the other hand, does not prevent activation but leads to a ten-fold diminution in the biological activity of the irradiated product (Windaus and Naggatz, *Annalen*, 1939, **542**, 209).

In a continuation of earlier work on the hydroxy-derivatives of cholesterol (Petrow and Starling, *J.*, 1940, 60; Petrow, Rosenheim, and Starling, *J.*, 1943, 135), we have now succeeded in preparing "α"-Δ^5-*cholesten*-3(β) : 4(β) : 7-*triol* (VI) and the corresponding C_7 epimeride, the "β"-*triol*. Our object was to attempt the dehydration of these compounds to $\Delta^{5:7}$-cholestadien-3(β) : 4(β)-diol and hence to determine the effect of introducing a hydroxyl-grouping on the structural changes associated with the irradiation of ring systems of this type.

Oxidation of 3(β) : 4(β)-dibenzoyloxy-Δ^5-cholestene (I; R = Bz) (Rosenheim and Starling, *J.*, 1937, 377) with chromic acid led to the formation of 3(β) : 4(β)-*dibenzoyloxy*-Δ^5-*cholesten*-7-*one* (II; R = Bz) in 70% yield, hydrolysis of which furnished Δ^5-*cholesten*-3(β) : 4(β)-*diol*-7-*one* (II; R = H). The constitution assigned to this compound was based upon the following experimental evidence: (*a*) the presence of a carbonyl group was shown by the formation of an *o*-*tolylsemicarbazone*, (*b*) the ultra-violet absorption curve showed a maximum



at 2380 A., log ϵ = 3·96, characteristic of $\alpha\beta$-unsaturated ketones, (*c*) on hypobromite oxidation it yielded 7-keto-Diels's acid (7-keto-Δ^5-cholesten-3‖4-diacid, Windaus, *Ber.*, 1908, **41**, 611) (III), further characterised by conversion into the monomethyl ester, and (*d*) the *cis*-configuration of the (β)-hydroxyl groups at C_3 and C_4 was confirmed by titration with lead tetra-acetate by Criegee's method. Oxidation of 3(β)-benzoyloxy-4(β)-acetoxy-Δ^5-cholestene gave likewise the 3(β)-*benzoyloxy*-4(β)-*acetoxy*-Δ^5-*cholesten*-7-*one*. The corresponding *diacetate* (II; R = Ac) was gelatinous and its manipulation difficult.

A re-examination of the reduction of 7-ketocholesterol by the Ponnsdorf–Meerwein method, first employed by Windaus, Lettré, and Schenk (*Annalen*, 1935, **520**, 98; U.S.P. 2,098,985) for the preparation of "7-hydroxycholesterol," was carried out by Wintersteiner and Ruigh (*J. Amer. Chem. Soc.*, 1942, **64**, 2453). These authors showed the latter product to be a mixture of two isomeric Δ^5-cholesten-3(β) : 7-diols, which differed in the configuration of the hydroxyls at C_7. The main constituent of the mixture, the "α"-diol, was slightly dextro-

* In this communication the letters "α" and "β" are used as prefixes in order to distinguish the two C_7 isomeric Δ^5-cholesten-3(β) : 7-diols [as well as the newly described Δ^5-cholesten-3(β) : 4(β) : 7-triols]. It must be stressed that in these compounds the configuration of the C_7 hydroxyl group with reference to the methyl group at C_{10} is not known. The use in the recent literature for such compounds of the designations (α) and (β) after the position numeral implies a definite stereochemical relationship for which there is at present no evidence (cf. *Ann. Reports*, 1938, 283).

rotatory, and its dibenzoate underwent facile pyrolysis in distinction from the dibenzoate of the lævo-rotatory " β "-diol.

We have now found that the reduction of 3(β) : 4(β)-dibenzoyloxy-Δ⁵-cholesten-7-one (II; R = Bz) with aluminium *iso*propoxide also gave a mixture which yielded on fractionation and benzoylation the weakly dextro-rotatory " α "-Δ⁵-*cholesten*-3(β) : 4(β) : 7-*triol* (VI) as the main product. A small quantity of the isomeric lævo-rotatory " β "-*triol*, " β "-Δ⁵-*cholesten*-3(β) : 4(β) : 7-*triol* was obtained with difficulty from the mother liquors. Both compounds were characterised by conversion into the *tribenzoates*.

Oxidation of " α "-3(β) : 7-dibenzoyloxy-Δ⁵-cholestene (IV) (Windaus *et al.*, *Annalen*, 1935, **520**, 98) with selenium dioxide gave " α "-3(β) : 7-*dibenzoyloxy*-Δ⁵-*cholesten*-4(β)-*ol* (V). Acetylation of this furnished " α "-3(β) : 7-*dibenzoyloxy*-4(β)*acetoxy*-Δ⁵-*cholestene*, whilst benzoylation gave the tribenzoate of " α "-Δ⁵-cholesten-3(β) : 4(β) : 7-triol identical with the compound previously described. Hydrolysis of these esters yielded the " α "-triol. These observations thus furnish experimental proof that the unknown configuration of the C_7 hydroxyl grouping in " α "-Δ⁵-cholesten-3(β) : 4(β) : 7-triol is identical with that in " α "-Δ⁵-cholesten-3(β) : 7-diol. Since the dibenzoate of the latter easily undergoes pyrolysis to the provitamin Δ⁵:⁷-cholestadien-3(β)-ol, it is surprising that we were unable to convert the tribenzoates of the " α "- and " β "-triols into the corresponding doubly-unsaturated steroid under a variety of experimental conditions. This failure may be associated with the ease with which acyl migration occurs in a similar system (cf. Petrow, Rosenheim, and Starling, *J.*, 1943, 135). Under the experimental conditions the Δ⁵-unsaturated 3 : 4 : 7-triol may have passed into a Δ⁴-3 : 6 : 7-triol and undergone complex changes on pyrolysis. This possibility is being investigated further. An allylic change of the type Δ⁵-cholesten-3 : 7-diol ⟶ Δ⁶-cholesten-3 : 5-diol, which occurs readily in acetic acid solution (Bergström and Wintersteiner, *J. Biol. Chem.*, 1941, **141**, 600; 1942, **143**, 503), is excluded by the fact that the triols are not affected under these experimental conditions.

Experimental.

M.p.'s are uncorrected. Microanalyses are by Drs. Weiler and Strauss, Oxford. Optical rotations were measured in chloroform solution in a 4 dm. tube.

3(β) : 4(β)-*Dibenzoyloxy*-Δ⁵-*cholesten*-7-*one* (II; R = Bz).—To a suspension of finely powdered 3(β) : 4(β)-dibenzoyloxy-Δ⁵-cholestene (15 g.) in glacial acetic acid (300 ml., stabilised) at 55—60°, was added dropwise with mechanical stirring over a period of 2 hours a solution of chromic acid (12 g.) in water (9 ml.) and glacial acetic acid (45 ml.). After a further 2 hours at this temperature excess of chromic acid was removed by addition of alcohol (8 ml.), and crystallisation induced by dropwise addition of water (65 ml.). After 12 hours at 0° the crystalline product (8·2 g.) was collected, washed with 80% acetic acid, and recrystallised from spirit (180 ml.). 3(β) : 4(β)-*Dibenzoyloxy*-Δ⁵-*cholesten*-7-*one* formed plates, m. p. 145—146°; $[\alpha]_D^{20°}$ −45·5°; $[\alpha]_{5461}^{20°}$ −53·6° (*c*, 1·12); a_{5461}/a_D = 1·18 (Found: C, 78·9; H, 8·1. $C_{41}H_{52}O_6$ requires C, 78·8; H, 8·4%). Yield 7 g.

The o-*tolylsemicarbazone*, needles from alcohol, m. p. 211—212° (Found: N, 5·6. $C_{48}H_{61}O_5N_3$ requires N, 5·4%), was prepared by heating a mixture of the solutions of the dibenzoate (100 mg.) in alcohol (2 ml.), and of *o*-tolylsemicarbazide (50 mg.) in alcohol (3 ml.) containing 3 drops of acetic acid, for 1½ hours under reflux.

3(β)-*Benzoyloxy*-4(β)-*acetoxy*-Δ⁵-*cholesten*-7-*one*.—Chromic acid (40 g.), in water (30 ml.) and glacial acetic acid (150 ml.), was added over 3 hours to the finely powdered 3(β)-benzoyloxy-4(β)-acetoxy-Δ⁵-cholestene (50 g.) (Rosenheim and Starling, *loc. cit.*), in glacial acetic acid (1 l.), at 60°. After a further hour excess of chromic acid was removed with alcohol, and, after 24 hours at room temperature, the product (m. p. 216°; 27 g.) was collected and recrystallised from acetone or dioxan–acetic acid (2 : 1). 3(β)-*Benzoyloxy*-4(β)*acetoxy*-Δ⁵-*cholesten*-7-*one* formed silky needles, m. p. 217—218°; $[\alpha]_D^{19°}$ −59·4°; $[\alpha]_{5461}^{19°}$ −68·6° (*c*, 1·364); a_{5461}/a_D = 1·14 (Found: C, 76·8; H, 8·8. $C_{36}H_{50}O_5$ requires C, 76·8; H, 8·9%).

Δ⁵-*Cholesten*-3(β) : 4(β)-*diol*-7-*one* (II; R = H).—To a suspension of finely powdered dibenzoate (5 g.) in boiling methanol (200 ml.), a solution of potassium hydrogen carbonate (5 g.) in water (20 ml.) was added. After 15 minutes under reflux, the yellow solution was treated with Norit, filtered, and poured into half-saturated salt solution (500 ml.). The cream-coloured product (3·8 g.) was extracted with ether and crystallised twice from acetone or methyl ethyl ketone, from which Δ⁵-*cholesten*-3(β) : 4(β)-*diol*-7-*one* slowly separated in colourless prismatic needles, m. p. 205—206°; $[\alpha]_D^{19°}$ −71·4°; $[\alpha]_{5461}^{19°}$ −86·8° (*c*, 1·088); a_{5461}/a_D = 1·2 (Found: C, 77·8; H, 10·7. $C_{27}H_{44}O_3$ requires C, 77·7; H, 10·6%). The compound separated on cooling its hot solutions in methanol, ethyl acetate, etc., as a transparent gel, which slowly changed into clusters of needles. The ultra-violet absorption spectrum showed a maximum at 2380 A., log ϵ_m = 3·96. After 2 hours at room temperature, 0·1004 g. of the keto-diol consumed 4·94 ml. of N/10-lead tetra-acetate solution, corresponding to 1·02 atoms of oxygen, and after 24 hours 0·1026 g. consumed 4·74 ml. (0·96 atom of oxygen). The o-*tolylsemicarbazone* formed silky needles from alcohol, m. p. 235—236° (Found: N, 7·3. $C_{35}H_{53}O_3N_3$ requires N, 7·5%).

7-*Keto*-Δ⁵-*cholesten*-3‖4-*diacid* (7-Keto-Diels's acid) (III).—The finely-powdered keto-diol (500 mg.) was added to potassium hypobromite, prepared by adding bromine (0·3 ml.) to a 25% solution of potassium hydroxide (5 ml.) and ice (4 g.), and the suspension mechanically shaken for 2 hours; a clear solution was then obtained. Excess of bromine was removed by sulphur dioxide and the acidified solution extracted with ether. The ether residue was crystallised from 90% acetic acid, from which the crude acid (300 mg.) separated in prisms, m. p. 215—217°. After purification as the sodium salt, which crystallised from 90% alcohol in needles, 7-keto-Diels's acid was obtained from dilute acetic acid in stout prisms, m. p. 216—218° [Found: C, 73·0; H, 9·0. Calc. for $C_{27}H_{42}O_5$: C, 72·9; H, 9·1%], not depressed in admixture with an authentic specimen. On titration, 0·3074 g. required 13·58 ml. of N/10-sodium hydroxide, corresponding to *M*, 452 (dibasic). Calc. for $C_{27}H_{42}O_5$: *M*, 446]. The characteristic monomethyl ester, shiny long prisms from methanol, m. p. 136—138° (*lit.* 136—137°), was obtained by dissolving the acid (85 mg.) in 5% methyl alcoholic sulphuric acid (2 ml.), from which the ester crystallised on slow evaporation overnight.

" α "-Δ⁵-*Cholesten*-3(β) : 4(β) : 7-*triol* (VI).—A solution of aluminium *iso*propoxide (45 g.) in *iso*propanol (600 ml.) was added to a suspension of powdered 3(β) : 4(β)-dibenzoyloxy-Δ⁵-cholesten-7-one [or 3(β)-benzoyloxy-4(β)-acetoxy-Δ⁵-cholesten-7-one] (20 g.) in *iso*propanol (500 ml.). The mixture was kept gently boiling and distilling for 6 hours as described by Lund (*Ber.*, 1937, **70**, 1520). Ether (500 ml.) was added to the cooled concentrated solution followed by 2N-sodium hydroxide (500 ml.). The washed and dried ethereal extract was concentrated by distillation, and the remaining solvent allowed to evaporate at room temperature. The collected crystalline deposits from three such preparations (30 g.) melted unsharply from 150° to 185°. The optical rotation, $[\alpha]_D$ −28°, of this mixture of 7-epimeric " α "- and

"β"-triols decreased on fractional crystallisation from ethyl acetate to $[\alpha]_D$ −4° for the top fraction, m. p. 185—189°, and rose to $[\alpha]_D$ −47° for the combined recrystallised fractions recovered from the mother liquors. These values remained substantially unchanged on further crystallisation from different solvents. Complete separation was effected by benzoylation of the top fraction (10 g.) in pyridine (150 ml.) with benzoyl chloride (8 ml.) at room temperature. After 24 hours water was added to the solution, previously diluted with alcohol, until crystallisation began. The product, m. p. 188—190°, was collected and recrystallised twice from acetone, from which "α"-3(β) : 4(β) : 7-*tribenzoyloxy*-Δ⁵-*cholestene* separated in needles, m. p. 190—192°; $[\alpha]_D^{18°}$ +99·6°; $[\alpha]_{5461}^{18°}$ +122·0° (*c*, 1·00); a_{5461}/a_D = 1·2 (Found: C, 78·5; H, 7·9. $C_{48}H_{56}O_6$ requires C, 78·9; H, 8·0%). For hydrolysis, a solution of the tribenzoate (500 mg.) in *n*-propanol (10 ml.) was heated under reflux with a solution of potassium *n*-propoxide, prepared from potassium (500 mg.) and *n*-propanol (10 ml.) (cf. Picard, Dissertation, Munich, 1935). After cooling in ice the crystalline precipitate of potassium benzoate was removed (Found: K benzoate, 349·3 mg. Calc. for tribenzoate: 336·2 mg.; for dibenzoate: 224·1 mg.). The triol (350 mg.) was recovered from the filtrate by careful addition of water. After two recrystallisations from 90% acetone, "α"-Δ⁵-*cholesten*-3(β) : 4(β) : 7-*triol* formed large prisms, m. p. 188—190°, $[\alpha]_D^{20°}$ +5·0° (*c*, 1·10) (Found: C, 77·6; H, 10·9. $C_{27}H_{46}O_3$ requires C, 77·4; H, 11·1%).

"β"-3(β) : 4(β) : 7-*Tribenzoyloxy*-Δ⁵-*cholestene*.—The mother liquors obtained on fractionation of the mixture of "α"- and "β"-triols (above) were concentrated and the combined products fractionated from ethyl acetate. After removal of the top fractions, consisting mainly of the "α"-triol, the remaining fractions (10 g.) were recrystallised several times from 90% alcohol and gave a product, m. p. 168—170°, $[\alpha]_D$ −47°. As no further separation was effected either by chromatography or by recrystallisation from different solvents, the product (4 g.) was benzoylated in pyridine solution as above. The resulting benzoates yielded on recrystallisation from acetone a small, less-soluble, fraction of "α"-3(β) : 4(β) : 7-tribenzoate, m. p. 188—190° (see above). The main fraction (3·5 g.), recovered from the mother liquors at *ca.* 0°, was twice recrystallised from alcohol, from which "β"-3(β) : 4(β) : 7-*tribenzoyloxy*-Δ⁵-*cholestene* separated in prisms, m. p. 150—152°; $[\alpha]_D^{20°}$ −45·0°; $[\alpha]_{5461}^{20°}$ −52·0° (*c*, 1·11); a_{5461}/a_D = 1·2 (Found: C, 78·5; H, 7·9. $C_{48}H_{56}O_6$ requires C 78·9; H, 8·0%).

"β"-Δ,⁵-*Cholesten*-3(β) : 4(β) : 7-*triol*, obtained by hydrolysis of the tribenzoate with potassium *n*-propoxide in *n*-propanol (see above), formed prisms from aqueous alcohol, m. p. 169—170°, forming liquid crystals at 130° (Koffler), $[\alpha]_D^{20°}$ −96·9° (*c*, 1·58) (Found: C, 77·8; H, 10·9. $C_{27}H_{46}O_3$ requires C, 77·4; H, 11·1%).

"α"-3(β) : 7-*Dibenzoyloxy*-Δ⁵-*cholesten*-4(β)-*ol* (V).—A solution of selenium dioxide (2 g.) in water (1 ml.) and glacial acetic acid (25 ml.) was added to a solution of "α"-3(β) : 7-dibenzoyloxy-Δ⁵-cholestene (5 g.) (Windaus *et al.*, *loc. cit.*) in dioxan (25 ml.) and the mixture heated on the water-bath. Separation of black selenium commenced within 3 minutes. After 5 hours' heating and the addition of sodium acetate (crystals, 1 g.), the solution was treated with Norit (500 mg.) and filtered. Water (5 ml.) was added dropwise to the filtrate; crystallisation then began, and, after 24 hours the product (3·5 g.) was collected. Selenium was removed from the yellowish combined products of three such preparations (10·5 g.) by pouring the solution in dioxan (30 ml.), under mechanical stirring, into 10% potassium cyanide solution (500 ml.). The resulting product, m. p. 185—190°, was fractionated from acetone–methanol (2 : 1). After removal of the top fraction (250 mg.; m. p. 174—176°), consisting of unchanged starting material, the fractions m. p. 192—195° were combined and repeatedly crystallised from chloroform–methanol (1 : 2), from which "α"-3(β) : 7-*dibenzoyloxy*-Δ⁵-*cholesten*-4(β)-*ol* separated in needles, m. p. 196—198°; $[\alpha]_D^{20°}$ +88·2°; $[\alpha]_{5461}^{20°}$ +103·1° (*c*, 1·04); a_{5461}/a_D = 1·17 (Found: C 78·6; H, 8·7. $C_{41}H_{54}O_5$ requires C, 78·6; H, 8·9%). Benzoylation by the usual technique yielded "α"-3(β) : 4(β) : 7-tribenzoyloxy-Δ⁵-cholestene, m. p. 188—190°, $[\alpha]_D^{15}$ +100·6° (*c*, 0·97), not depressed in admixture with the product described above. Hydrolysis of the tribenzoate with potassium *n*-propoxide in *n*-propanol (see above) gave "α"-Δ⁵-cholesten-3(β) : 4(β) : 7-triol, m. p. 188—190° alone or in admixture with the "α"-triol obtained by reduction of 3(β) : 4(β)-dibenzoyloxy-Δ⁵-cholesten-7-one.

"α"-3(β) : 7-*Dibenzoyloxy*-4(β)-*acetoxy*-Δ⁵-*cholestene*.—A solution of "α"-3(β) : 7-dibenzoyloxy-Δ⁵-cholesten-4(β)-ol (270 mg.) in pyridine (2 ml.) was heated with acetic anhydride (1 ml.) for 40 minutes on the water-bath. The product (290 mg.) was twice crystallised from acetone, from which "α"-3(β) : 7-*dibenzoyloxy*-4(β)-*acetoxy*-Δ⁵-*cholestene* separated in prismatic needles, m. p. 231—233°; $[\alpha]_D^{19°}$ +68·1°; $[\alpha]_{5461}^{19°}$ +84·2° (*c*, 1·09); a_{5461}/a_D = 1·2 (Found: C, 77·2; H, 8·4. $C_{43}H_{56}O_6$ requires C, 77·2; H, 8·4%).

The authors' thanks are due to Prof. C. Rimington, University College Hospital Medical School, W.C.1., for the hospitality of his laboratory during the final stages of this research, and to Mr. F. A. Robinson, M.Sc., F.R.I.C., and Glaxo Laboratories Ltd. for a gift of "α"-3 : 7-dibenzoyloxy-Δ⁵-cholestene.

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155. *The Preparation of* N⁴*-Carboxyacylsulphonamides. Part I. Reactions of Succinimidobenzenesulphonyl Chloride and Succinylsulphanilyl Chloride.*

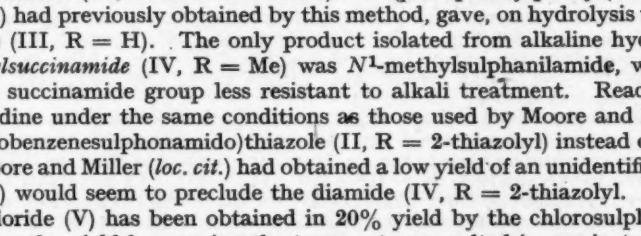
By C. W. Picard, E. Reid, and D. E. Seymour.

p-Succinimidobenzenesulphonyl chloride (I) has been condensed with a number of amines to yield the corresponding *p*-succinimidobenzenesulphonamides which have been hydrolysed to the corresponding N⁴-succinylsulphanilamides. Succinylsulphanilyl chloride (V) has been prepared and condensed with ammonia, methylamine, and aniline to yield the corresponding N⁴-succinylsulphanilamides (III). The condensation of succinylsulphanilyl chloride with aminoheterocyclic compounds does not proceed smoothly.

N⁴-Succinylsulphanilamides are normally obtained by the reaction of succinic acid, anhydride, or ester with a sulphanilamide (*e.g.*, B.P. 515,412; B.P. 557,985; U.S.P. 2,323,651; Miller, Rock, and Moore, *J. Amer. Chem. Soc.*, **1939**, **61**, 1198; Shapiro and Bergmann, *J. Org. Chem.* **1941**, **6**, 774; Moore and Miller, *J. Amer. Chem. Soc.*, **1942**, **64**, 1572). The use of *p*-succinimidobenzenesulphonyl chloride (I) as a means of preparing such compounds has received little attention, and *succinylsulphanilyl chloride* (V) does not appear to have been previously described in the literature apart from a German patent (D.R.P. 731,912) which mentions the use of the crude sulphonyl chloride in a preparation of succinylsulphapyridine, but gives no details of its method of preparation or properties.

p-Succinimidobenzenesulphonyl chloride (I) (Adams, Long, and Jeans, *J. Amer. Chem. Soc.*, 1939, **61**, 2346; Moore and Miller, *loc. cit.*) has been caused to react with amines under two series of conditions: (*a*) with one molecular proportion of amine (ammonia, methylamine, aniline, 2-aminopyridine, or 2-aminothiazole) in the presence of pyridine or a second mol. of the reacting amine acting as acid acceptor, to give the corresponding *p*-succinimidobenzenesulphonamide (II) in good yield. On hydrolysis with sodium hydroxide the imide ring was readily opened to give the corresponding N^4-succinylsulphanilamide (III); (*b*) with excess of ammonia or methylamine to give the diamide (IV, R = H or R = Me). *N*-(*p*-Sulphamylphenyl(succinamide (IV, R = H), which Adams *et al.* (*loc. cit.*) had previously obtained by this method, gave, on hydrolysis with sodium hydroxide, N^4-succinylsulphanilamide (III, R = H). The only product isolated from alkaline hydrolysis of N-(p-*methylsulphamylphenyl*)-N′-*methylsuccinamide* (IV, R = Me) was N^1-methylsulphanilamide, which suggests that the methyl group renders the succinamide group less resistant to alkali treatment. Reaction of (I) with excess of 2-aminothiazole in pyridine under the same conditions as those used by Moore and Miller (*loc. cit.*) gave in good yield 2-(*p*-succinimidobenzenesulphonamido)thiazole (II, R = 2-thiazolyl) instead of the expected diamide (IV, R = 2-thiazolyl); Moore and Miller (*loc. cit.*) had obtained a low yield of an unidentified product the nitrogen analysis of which (14·85%) would seem to preclude the diamide (IV, R = 2-thiazolyl. Calc.: N, 16·0%).

Succinylsulphanilyl chloride (V) has been obtained in 20% yield by the chlorosulphonation of succinanilic acid. Attempts to improve the yield by varying the temperature resulted in one instance in the formation of *p*-succinimidobenzenesulphonyl chloride (I) in low yield. Treatment of succinylsulphanilyl chloride with acetyl chloride gave *p*-succinimidobenzenesulphonyl chloride. The sulphonyl chloride (V) has been condensed with ammonia to give succinylsulphanilamide (III, R = H); with methylamine to give N^4-*succinyl*-N^1-*methylsulphanilamide* (III, R = Me); and with aniline to give N^4-*succinyl*-N^1-*phenylsulphanilamide* (III, R = Ph). In each case an excess of the condensing amine was used as acid acceptor. Satisfactory conditions for the condensation of succinylsulphanilyl chloride with amino-heterocyclic compounds have not so far been devised.



Experimental.

All m. ps. are uncorrected. Analyses by Drs. Weiler and Strauss.

p-Succinimidobenzenesulphonyl chloride (I) was prepared by chlorosulphonation of succinanil (Adams *et al.*, *loc. cit.*) and purified by dissolving the wet sulphonyl chloride in acetone and reprecipitating it (with cooling) by water. It separated from the aqueous acetone as white needles, m. p. 197·5—198·5° (yield 48%). Moore and Miller (*loc. cit.*) give 189—195° (Found: C, 44·05; H, 2·9; N, 5·2. Calc. for $C_{10}H_8O_4NClS$: C, 43·9; H, 2·95; N, 5·1%). When treated with excess of ammonia under the conditions of Adams *et al.* (*loc. cit.*) it gave *N*-(*p*-sulphamylphenyl)succinamide (IV, R = H) as needles from water, m. p. 237—237·5°. Adams *et al.* (*loc. cit.*) give m. p. 234—238° (Found: C, 44·3; H, 4·95; N, 15·5. Calc. for $C_{10}H_{13}O_4N_3S$: C, 44·3; H, 4·85; N, 15·5%). With excess of methylamine under similar conditions N-(p-*methylsulphamylphenyl*)-N′-*methylsuccinamide* (IV, R = Me), m. p. 204—205°, was obtained as needles from water (Found: C, 48·55; H, 5·8; N, 13·9. $C_{12}H_{17}O_4N_3S$ requires C, 48·2; H, 5·75; N, 14·05%).

N-(*p*-Sulphamylphenyl)succinamide (IV, R = H) (1·1 g.) was hydrolysed by boiling with aqueous potassium hydroxide (0·25 N; 16 ml.) for 2½ hours; on neutralisation with hydrochloric acid (Congo red), N^4-succinylsulphanilamide (0·35 g.) was obtained as needles from water, m. p. 207—209° (Found: C, 44·4; H, 4·4; N, 10·5. Calc. for $C_{10}H_{12}O_5N_2S$: C, 44·15; H, 4·45; N, 10·3%). Under similar conditions *N*-(*p*-methylsulphamylphenyl)-*N*′-methylsuccinamide gave a low yield of N^1-methylsulphanilamide as needles from water, m. p. 109—109·5° (cf. Mangini, *Chem. Abs.*, 1943, **37**, 98).

p-*Succinimidobenzenesulphonamide* (II, R = H).—A solution of the sulphonyl chloride (I) (2·75 g.; 0·01 mol.) in acetone (30 ml.) and pyridine (2 ml.) was shaken with ammonia (*d*, 0·88; 0·57 ml.; 0·01 mol.) for 15 minutes, and the solid which separated was removed and washed with water (0·58 g.; m. p. 279—283°). Recrystallisation from water gave *p*-succinimidobenzenesulphonamide as needles, m. p. 290—290·5° undepressed by admixture with a specimen (m. p. 290—290·5°) prepared according to the method of Miller, Rock, and Moore (*loc. cit.*) who give m. p. 280—282° (Found: C, 47·3; H, 4·0; N, 10·9. Calc. for $C_{10}H_{10}O_4N_2S$: C, 47·3; H, 3·95; N, 11·05%). The compound (II, R = H) (0·42 g.) was hydrolysed by heating under reflux for 1 hour with potassium hydroxide solution (0·5 N; 3·33 ml.). After being cooled, the solution was neutralised with hydrochloric acid and the precipitated solid (0·4 g.), m. p. 204—206°, recrystallised from water to give N^4-succinylsulphanilamide as needles, m. p. 209—211° undepressed with a specimen (m. p. 212—212·5°) obtained according to the conditions of Miller, Rock, and Moore (*loc. cit.*).

N-(p-*Methylsulphamylphenyl*)*succinimide* (II, R = Me).—*p*-Succinimidobenzenesulphonyl chloride (2·74 g.; 0·01 mol.) in acetone (50 ml.) was treated with methylamine solution (33% w/v; 1·88 ml.; 0·02 mol.). The mixture was shaken for 15 minutes and refluxed for 15 minutes, and the acetone was then removed and the residue triturated with water and crystallised from aqueous alcohol (1 : 1) to give N-(p-*methylsulphamylphenyl*)*succinimide* as needles (1·1 g.), m. p. 199—199·5° (Found: C, 49·05; H, 4·4; N, 10·3. $C_{11}H_{12}O_4N_2S$ requires C, 49·3; H, 4·5; N, 10·45%). The compound (0·7 g.) was hydrolysed by boiling for 1½ hours with potassium hydroxide solution (0·1 N; 50 ml.) to give N^1-methyl-N^4-succinylsulphanilamide (III, R = Me) as plates from alcohol (0·6 g.), m. p. 207—207·5° undepressed with a specimen prepared as described below.

p-*Succinimidobenzenesulphonanilide* (II, R = Ph).—*p*-Succimidobenzenesulphonyl chloride (4·09 g.; 0·015 mol.) was heated with aniline (1·4 g.; 0·015 mol.) in pyridine (13 ml.) at 100° for 1 hour. Excess of water was added and the product (4·3 g.), m. p. 246—246·5°, was recrystallised from glacial acetic acid to give p-*succinimidobenzenesulphonanilide* as needles, m. p. 248—249° (Found: C, 58·15; H, 4·6; N, 8·75. $C_{16}H_{14}O_4N_2S$ requires C, 58·25; H, 4·3; N, 8·5%). The sulphonanilide (0·33 g.) was refluxed with potassium hydroxide solution (0·1 N; 25 ml.) for 1 hour. Neutralisation with hydrochloric acid gave N^1-phenyl-N^4-succinylsulphanilamide (III, R = Ph) (0·25 g.), m. p. 223—224° undepressed when mixed with the specimen described below.

2-(p-*Succinimidobenzenesulphonamido*)*pyridine* (II, R = 2-pyridyl).—A solution of 2-aminopyridine (0·95 g.; 0·01 mol.) in pyridine (10 ml.) was heated for 30 minutes on the steam-bath with *p*-succinimidobenzenesulphonyl chloride (2·749 g.; 0·01 mol.). The mixture was cooled, and water (50 ml.) was added and the solid collected (2·8 g.; m. p. 262—271°). Recrystallisation from acetic acid (40%) gave 2-(*p*-succinimidobenzenesulphonamido)pyridine, m. p. 288—289°. Shapiro and Bergmann (*loc. cit.*) give m. p. 288—290° for the compound prepared by condensation of succinic anhydride with sulphapyridine (Found: C, 54·3; H, 4·1; N, 12·7. Calc. for $C_{15}H_{13}O_4N_3S$: C, 54·45; H, 3·95; N, 12·7%). The compound (II, R = 2-pyridyl) (0·83 g.) was refluxed for 2 hours with potassium hydroxide solution (0·1N; 50 ml.); N^4-succinylsulphapyridine was obtained as needles from alcohol (0·4 g.), m. p. 196—197° (Found: C, 51·65; H, 5·55; N, 10·4. Calc. for $C_{15}H_{15}O_5N_3S,C_2H_6O$: C, 51·65; H, 5·35; N, 10·65%). For comparative purposes, 2-(*p*-succinimidobenzenesulphonamido)pyridine was prepared as described by Shapiro and Bergmann (*loc. cit.*). The product separated as needles from alcohol, m. p. 195—196° undepressed when mixed with the specimen described above (Found: C, 51·7; H, 5·5; N, 10·8%). Shapiro and Bergmann obtained a product free from solvent of crystallisation, m. p. 145°; Moore and Miller give m. p. 135—140° rising to 191—194° after seven months, whilst D.R.P. 731,912 gives m. p. 191°. The solvent of crystallisation was not removed from our product by drying in a high vacuum at 80°.

2-(p-*Succinimidobenzenesulphonamido*)*thiazole* (II, R = 2-thiazolyl).—2-Aminothiazole (5 g.; 0·05 mol.) in pyridine (50 ml.) was treated with *p*-succinimidobenzenesulphonyl chloride (13·65 g.; 0·05 mol.) with shaking. The mixture was then heated at 100° for 1 hour and the pyridine removed under reduced pressure. The residue was triturated with water (100 ml.) to yield a brown powder, m. p. 252—255° (13·3 g.). The crude material was washed and recrystallised several times from aqueous dioxan (1 : 1) (charcoal) to yield white needles, m. p. 269·5—270·5° (2·2 g.). Moore and Miller (*loc. cit.*) give m. p. 266—267° for this compound prepared by a different method (Found: C, 46·4; H, 3·5; N, 12·5. Calc. for $C_{13}H_{11}O_4N_3S_2$: C, 46·35; H, 3·3; N, 12·5%). The same compound (II, R = 2-thiazolyl) was obtained when two equivalents of 2-aminothiazole were used (*a*) in pyridine solution (cf. Moore and Miller, *loc. cit.*) and (*b*) in benzene solution. The anil (II, R = 2-thiazolyl) was also obtained from N^4-succinylsulphathiazole by heating with acetyl chloride or by heating at its m. p. for 10 minutes. The anil was hydrolysed with boiling aqueous potassium hydroxide solution (2 equivs.; 0·1 N) to give N^4-succinylsulphathiazole as needles from aqueous alcohol, m. p. 186—187° [Found (for specimen dried at 80°/15 mm.): C, 42·2; H, 4·05; N, 11·5; (for specimen dried at 80° in high vacuum): C, 43·85; H, 3·8; N, 11·6. Calc. for $C_{13}H_{13}O_5N_3S_2,H_2O$: C, 41·85; H, 4·05; N, 11·25. Calc. for $C_{13}H_{13}O_5N_3S_2$: C, 44·0; H, 3·7; N, 11·85%].

Succinylsulphanilyl chloride (V) was prepared by adding succinanilic acid (19·3 g.) to chlorosulphonic acid (33 ml.) at 10—12°. The temperature was then maintained at 40—50° for 40 hours with agitation by means of nitrogen bubbles. The crude sulphonyl chloride was precipitated by pouring on crushed ice (200 g.). The product was washed and purified by dissolving in acetone (80 ml.) and reprecipitating with water (250 ml., added slowly with cooling). A crystalline solid, m. p. 142—143° (8 g.; 42%), separated which was recrystallised from acetone–benzene (1 : 9; 500 ml.) to give needles, m. p. 142—143° (3·8 g.; 20%) (Found: C, 41·7; H, 3·65; N, 5·15. $C_{10}H_{10}O_5NClS$ requires C, 41·2; H, 3·45; N, 4·8%). The sulphonyl chloride (5 g.) was refluxed with acetyl chloride (15 ml.) for 15 minutes to give *p*-succinimidobenzenesulphonyl chloride as needles from aqueous acetone, m. p. 197—198° (2·8 g.).

N^4-*Succinylsulphanilamide* (III, R = H).—Succinylsulphanilyl chloride (0·4 g.) was added to ice-cold ammonia (*d* 0·88; 5 ml.). An oil separated which redissolved on shaking. After being kept at 0° for 2 hours the solution was acidified with dilute hydrochloric acid and the solid (m. p. 188—191·5°; 0·4 g.) collected and crystallised from water to give needles, m. p. 209—210° (Found: C, 44·5; H, 4·6; N, 10·1. Calc. for $C_{10}H_{11}O_5N_3S$: C, 44·15; H, 4·45; N, 10·3%).

N^4-*Succinyl*-N^1-*methylsulphanilamide* (III, R = Me).—Succinylsulphanilyl chloride (1·47 g.; 0·005 mol.) was stirred for 2 hours with a solution of methylamine hydrochloride (6·75 g.; 0·1 mol.) in water (15 ml.) containing sodium carbonate (5·3 g.). The crystalline solid, m. p. 198—201° (1·0 g.), was collected and recrystallised from water to give N^4-*succinyl*-N^1-*methylsulphanilamide* as needles, m. p. 204—205° (Found: C, 46·55; H, 4·95; N, 10·1. $C_{11}H_{14}O_5N_3S$ requires C, 46·2; H, 4·95; N, 9·8%).

N^4-*Succinyl*-N^1-*phenylsulphanilamide* (III, R = Ph).—Succinylsulphanilyl chloride (1·47 g.; 0·005 mol.) was refluxed for 1 hour with a solution of aniline (1·16 g.; 0·0125 mol.) in benzene (15 ml.). The benzene was then removed and the residue triturated with water to yield a white solid (3 g.; m. p. 178—179°). Repeated crystallisation from aqueous alcohol gave needles of N^4-*succinyl*-N^1-*phenylsulphanilamide*, m. p. 223—224° (0·8 g.). (Found: C, 55·1; H, 4·8; N, 7·9. $C_{16}H_{16}O_5N_2S$ requires C, 55·2; H, 4·65; N, 8·05%).

The authors are indebted to Miss J. Reynolds for carrying out a considerable part of the experimental work and to Dr. F. S. Spring of Manchester University for his interest and advice. They also thank the Directors of Herts Pharmaceuticals Limited for permission to publish this work.

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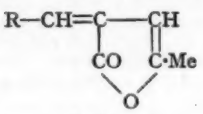
NOTES.

The Production of Coumarin Derivatives by Condensation of o-Hydroxy-aldehydes with $\Delta^{\beta\gamma}$*-Angelicalactone.*

By D. H. MARRIAN and P. B. RUSSELL.

THIELE, TISCHBEIN, and LÖSSOW (*Annalen*, 1901, **319**, 185) condensed $\Delta^{\beta\gamma}$-angelicalactone with benzaldehyde and anisaldehyde in presence of diethylamine and showed that under these conditions benzaldehyde yielded α-benzylidene-laevulic acid cyclised by heating with acetic anhydride and a little sulphuric acid to γ-methyl-α-benzylidene-$\Delta^{\beta\gamma}$-butenolide (I; R = Ph); anisaldehyde yielded the corresponding α-anisylidene lactone (I; R = *p*-MeO·C_6H_4) directly. More recently von Oettingen (*J. Amer. Chem. Soc.*, 1930, **52**, 2024) condensed a series of aldehydes including salicyl-

aldehyde and β-resorcylaldehyde under similar conditions with $\Delta^{\beta\gamma}$-angelicalactone and obtained products to which he ascribed structures of type (I).



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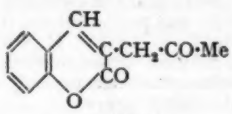


(II.)

In the course of other investigations in this laboratory we had occasion to condense a series of aromatic aldehydes with $\Delta^{\beta\gamma}$-angelicalactone. We observed that the products from *o*-hydroxy-aldehydes differed considerably in their properties from the others. They gave analytical values in agreement with those expected for structure (I), but were almost colourless and, as had been observed by von Oettingen (*J. Pharm.*, 1930, **39**, 59), were unexpectedly soluble in water. Moreover, they were ketonic and gave semicarbazones and 2 : 4-dinitrophenylhydrazones under normal conditions; compounds such as (I; R = *p*-MeO·C_6H_4) failed to react with ketone reagents under similar conditions.

When refluxed with methanolic potassium hydroxide, the condensation product of salicylaldehyde and $\Delta^{\beta\gamma}$-angelicalactone gave a deep yellow solution from which by acidification the original substance could be recovered unchanged; Thiele, Tischbein, and Lössow (*loc. cit.*) showed that (I; R = *p*-MeO·C_6H_4) gave on similar treatment α-anisylidenelaevulic acid. The condensation product gave a positive iodoform reaction and on oxidation with dichromate gave coumarin-3-carboxylic acid. We therefore conclude that the condensation product is, in fact, 3-*acetonylcoumarin* (II). In the same way, the condensation of $\Delta^{\beta\gamma}$-angelicalactone with β-resorcylaldehyde gives 7-hydroxy-3-acetonylcoumarin and with 2-hydroxy-1-naphthaldehyde 3-*acetonyl*-5 : 6-*benzocoumarin*. Formation of coumarin derivatives by this means is presumably a general property of *o*-hydroxy-aldehydes. These findings incidentally vitiate certain conclusions drawn by von Oettingen (*J. Pharm., loc. cit.*) as to the relationship between anthelmintic properties and chemical constitution of the products from salicylaldehyde and β-resorcylaldehyde.

3-*Acetonylcoumarin*.—Salicylaldehyde (6·1 g.) condensed with $\Delta^{\beta\gamma}$-angelicalactone (4·9 g.) in presence of triethylamine (20 drops) gave colourless needles of 3-*acetonylcoumarin*, m. p. 97—98°; von Oettingen (*J. Amer. Chem. Soc., loc. cit.*) gives m. p. 96° for "α-salicylal-Δ_2-angelica lactone" (Found : C, 71·0; H, 5·0. $C_{13}H_{10}O_3$ requires C, 71·3; H, 4·9%). The product gave a *semicarbazone* separating from glycol monomethyl ether in colourless prisms, m. p. 234—235° (decomp.) (Found : N, 15·8. $C_{13}H_{13}O_3N_3$ requires N, 16·2%). The 2 : 4-*dinitrophenylhydrazone*, dark red needles from glycol monomethyl ether, had m. p. 199·5—200·5° (Found : N, 14·5. $C_{19}H_{14}O_6N_4$ requires N, 14·6%).

The above product (0·5 g.) was dissolved in acetic acid (5 c.c.), aqueous potassium dichromate (0·857 g. in 10 c.c.) acidified with sulphuric acid added, and the mixture left overnight then warmed on the steam-bath for 30 mins. The resulting solution was diluted with water (50 c.c.) and concentrated under reduced pressure to remove most of the acetic acid. The colourless crystalline solid which separated had m. p. 189—190° undepressed in admixture with coumarin-3-carboxylic acid (m. p. 189—191°) prepared according to Knoevenagel (*Ber.*, 1898, **31**, 2619) (Found : C, 63·5; H, 3·4. Calc. for $C_{10}H_6O_4$: C, 63·2; H, 3·1%).

7-*Hydroxy*-3-*acetonylcoumarin*.—The condensation of β-resorcylaldehyde with $\Delta^{\beta\gamma}$-angelicalactone gave as described by von Oettingen (*J. Amer. Chem. Soc., loc. cit.*) colourless plates, m. p. 167—168°. The product yielded a colourless *semicarbazone*, m. p. 245—246° (decomp.) (Found : N, 15·4. $C_{13}H_{13}O_4N_3$ requires N, 15·3%), and an orange 2 : 4-*dinitrophenylhydrazone*, m. p. 253—254° (Found : N, 13·8. $C_{19}H_{14}O_7N_4$ requires N, 14·1%).

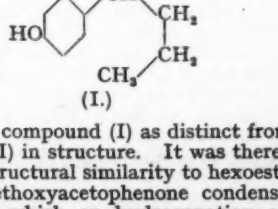
3-*Acetonyl*-5 : 6-*benzocoumarin*.—Triethylamine (5 drops) was added to a mixture of 2-hydroxy-1-naphthaldehyde (1·7 g.) and $\Delta^{\beta\gamma}$-angelicalactone (0·98 g.); heat was evolved and water separated at once. After having been warmed for a few minutes the whole mass set solid and was recrystallised from benzene giving the *compound* in faintly yellowish plates, m. p. 167°, which dissolved in methanol with a blue fluorescence and gave no coloration with ferric chloride (Found : C, 76·0; H, 5·1. $C_{16}H_{12}O_3$ requires C, 76·2; H, 4·7%). The substance yielded a *semicarbazone* crystallising from aqueous pyridine in colourless needles, m. p. 232° (decomp.) (Found : N, 13·4. $C_{17}H_{15}O_3N_3$ requires N, 13·6%), and a 2 : 4-*dinitrophenylhydrazone* forming orange needles, m. p. 188—189°, from aqueous acetic acid (Found : N, 13·3. $C_{22}H_{16}O_6N_4$ requires N, 13·0%).

The authors wish to thank Professor A. R. Todd, F.R.S., for his interest in this work and to express their indebtedness to the Agricultural Research Council for research grants.—UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, December 20th*, 1945.]

1-(m-*Hydroxyphenyl*)-3-(p-*hydroxyphenyl*)*hexane and* 1-(m-*Hydroxyphenyl*)-3-(p-*hydroxyphenyl*)*hexene*.

By B. J. F. HUDSON.

IN the course of recent investigations of a number of substituted 1 : 3-di-(*p*-hydroxyphenyl)propanes Stuart and Tallman (*J. Amer. Chem. Soc.*, 1943, **65**, 1579) have prepared 1 : 3-di-(*p*-hydroxyphenyl)hexane (I) and shown it to possess oestrogenic activity of a low order.



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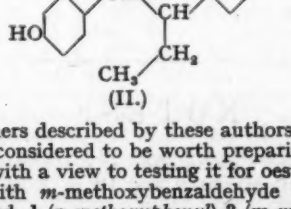

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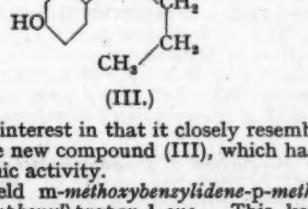

(III.)

This compound (I) as distinct from others described by these authors is of interest in that it closely resembles hexoestrol (II) in structure. It was therefore considered to be worth preparing the new compound (III), which has an even closer structural similarity to hexoestrol, with a view to testing it for oestrogenic activity.

p-Methoxyacetophenone condensed with *m*-methoxybenzaldehyde to yield m-*methoxybenzylidene*-p-*methoxyacetophenone* which on hydrogenation afforded 1-(p-*methoxyphenyl*)-3-(m-*methoxyphenyl*)*propan*-1-*one*. This ketone was treated with *n*-propylmagnesium iodide, and the product dehydrated to form a substituted hexene, which on demethylation with methylmagnesium iodide gave 1-(m-*hydroxyphenyl*)-3-(p-*hydroxyphenyl*)*hexene* (IV). The position of the double bond in these last two compounds is uncertain. On hydrogenation the methyl ether of (IV) gave an oily reduction product from which 1-(m-*hydroxyphenyl*)-3-(p-*hydroxyphenyl*)*hexane* (III) was obtained in crystalline form by demethylation.

Biological assay of compounds (III) and (IV) was carried out by Mr. A. F. Green of the Wellcome Physiological Research Laboratories, Beckenham. They were shown by the uterine weight method in rats to have less than one-thousandth of the activity of stilboestrol.

m-*Methoxybenzylidene*-p-*methoxyacetophenone*.—A mixture of *m*-methoxybenzaldehyde (34·1 g.) and *p*-methoxyacetophenone (37·6 g.) was treated cautiously with a solution of sodium (0·75 g.) in methanol (75 c.c.). After 24 hours the crystalline precipitate was collected, washed with methanol and water, and dried. 49·2 G. of material, m. p. 91—96°, were obtained. On recrystallisation the pure *product* separated from methanol in clusters of minute pale yellow leaflets, m. p. 96—97° (Found: C, 75·7; H, 6·5. $C_{17}H_{16}O_3$ requires C, 76·1; H, 6·0%).

1-(p-*Methoxyphenyl*)-3-(m-*methoxyphenyl*)*propan*-1-*one*.—The substituted chalkone (49 g.) was hydrogenated in ethyl acetate solution (240 c.c.) in the presence of Adams's platinic oxide catalyst (0·5 g.) at two atmospheres. After the completion of absorption of hydrogen, the catalyst was separated and the filtrate evaporated. The residual *oil* crystallised from chilled methanol in stout needles, m. p. 49—51° (Found: C, 75·8; H, 7·1. $C_{17}H_{18}O_3$ requires C, 75·5; H, 6·7%).

1-(m-*Methoxyphenyl*)-3-(p-*methoxyphenyl*)-Δ^2 (*and/or* Δ^3)-*hexene*.—The foregoing ketone (21·6 g.) was added slowly to the Grignard reagent prepared from magnesium (2·16 g.) and *n*-propyl iodide (17 g.) in dry ether (150 c.c.). After 12 hours the reaction mixture was worked up in the usual manner and an oily carbinol, presumably 1-(*m*-methoxyphenyl)-3-(*p*-methoxyphenyl)hexan-1-ol, obtained.

This material was dehydrated by the action of a saturated solution of hydrogen chloride in acetic acid (80 c.c.) in the course of 48 hours. The product, on distillation in a vacuum, was a colourless mobile oil (18·0 g.), b. p. 204—208°/3—4 mm.

1-(m-*Hydroxyphenyl*)-3-(p-*hydroxyphenyl*)-Δ^2(*and/or* Δ^3)-*hexene* (IV).—The oily methyl ether (7·4 g.) was mixed with a Grignard reagent prepared from magnesium (1·43 g.) and methyl iodide (9 g.) in dry ether (50 c.c.). The ether was distilled off, and the residue cautiously heated up to 175° for one hour, by which time frothing had ceased and a brittle melt had formed. This was decomposed with ice and dilute sulphuric acid, and the oily phenol extracted with ether. The *product* was a hard "glass" (4·9 g.), b. p. 250°/5 mm. (Found: C, 79·9; H, 7·4. $C_{18}H_{20}O_2$ requires C, 80·55; H, 7·5%).

1-(m-*Methoxyphenyl*)-3-(p-*methoxyphenyl*)*hexane*.—The oily unsaturated methyl ether (above) (10·0 g.) was hydrogenated in acetone (25 c.c.) solution in the presence of palladised charcoal (4·0 g.). After separation of the catalyst the solution was evaporated and the residual oil distilled in a vacuum. There were obtained 8·8 g., b. p. 200—201°/2 mm., of a colourless mobile oil.

1-(m-*Hydroxyphenyl*)-3-(p-*hydroxyphenyl*)*hexane* (III).—The above methyl ether (9·0 g.) was demethylated by heating under reflux for one hour with acetic acid (72 c.c.) and hydriodic acid (*d* 1·7, 36 c.c.). The product was worked up in the usual manner and afforded a light orange "glass," b. p. 250—260°/10 mm. After nine months this *substance* almost completely solidified. It was recrystallised from carbon tetrachloride, and separated in soft white leaflets, m. p. 80—82° (Found: C, 79·6; H, 8·2. $C_{18}H_{22}O_2$ requires C, 80·0; H, 8·2%).

All m. p.'s are uncorrected.

Thanks are due to the Wellcome Foundation Ltd. for permission to publish, to Mr. A. Bennett for analyses, and to Dr. E. Walton for his interest in this work.—Wellcome Chemical Works, Dartford. [*Received, December 15th*, 1945.]

Ethyl Ketoglutaconate. By J. W. Cornforth and R. H. Cornforth.

This substance, $CO_2Et{\cdot}CH{:}CH{\cdot}CO{\cdot}CO_2Et$, has been obtained in poor yield by oxidation of ethyl glutaconate with selenium dioxide. Its ultra-violet absorption has been measured.

A mixture of ethyl glutaconate (12 g.), selenium dioxide (7 g.), and acetic acid (60 c.c.) was boiled under reflux for 45 minutes, the selenium removed, and the solvent evaporated under low pressure. After being washed in ether with sodium bicarbonate solution the product was distilled, giving 3 g., b. p. *ca.* 100°/1 mm. This was redistilled and collected up to 95°/0·1 mm.; the distillate was treated with sodium bisulphite solution (5 c.c.; saturated). After a few minutes the crystalline adduct was collected, washed with ether, and decomposed by cautious brief warming with dilute sulphuric acid. The oil was isolated in the usual manner and distilled, giving *ethyl ketoglutaconate* as a light yellow mobile liquid (0·25 g.), b. p. 93°/0·1 mm. (Found: C, 54·0; H, 6·3. $C_9H_{12}O_5$ requires C, 54·0; H, 6·0%). It reacted instantly with sodium bisulphite solution to form a colourless crystalline mass.

The 2 : 4-*dinitrophenylhydrazone* separated from alcohol as deep yellow lustrous leaflets, m. p. 147—148° (Found: C, 47·3; H, 4·4. $C_{15}H_{16}O_8N_4$ requires C, 47·4; H, 4·2%). In an earlier oxidation conducted in toluene the 2 : 4-dinitrophenylhydrazone, prepared from the crude first distillate, was obtained in red needles from alcohol, m. p. 145—146° (Found: C, 47·4; H, 4·0%). Both forms melted to a bright green liquid.

The absorption spectrum in ether, measured by Dr. F. B. Strauss, showed $\lambda_{max.} = 2280$ A., $\epsilon^{molar}_{max.} = 9730$. In methanol ϵ^{molar} was 3670 at 2290 A., and no carbonyl band was found, indicating addition of methanol to the keto group.—Dyson Perrins Laboratory, Oxford. [*Received, February 27th*, 1946.]

Some New Glycol Mono-ethers. By W. J. Dunstan.

In the course of work on bacteriostatic action certain glycol mono-ethers and derivatives were required, and the following appear to be new: (1) 2-p-*methoxyphenoxyethanol* and its p-*nitrobenzoate*; (2) 2-o-*hydroxymethylphenoxyethanol*; (3) p-*nitrobenzoate* of 2-*p*-bromophenoxyethanol.

The glycols were prepared in the usual manner, using ethylene chlorohydrin, sodium ethoxide, and the requisite phenol (Bentley, Haworth, and Perkin, *J.*, 1896, **69**, 164). The *p*-nitrobenzoates were prepared by treating a solution of the substance in dry pyridine with *p*-nitrobenzoyl chloride.

Compound (1) formed white needles, m. p. 70°, from light petroleum (b. p. 60—80°); yield 45% (Found: C, 64·5; H, 7·25. $C_9H_{12}O_3$ requires C, 64·25; H, 7·2%). Its *p*-nitrobenzoate formed pale yellow plates, m. p. 96°, from alcohol (Found: C, 60·5; H, 4·8. $C_{16}H_{15}O_6N$ requires C, 60·5; H, 4·8%).

Compound (2) was isolated as an oil which solidified on standing. Attempts to recrystallise it from carbon tetrachloride gave an oil which solidified on the addition of a drop of water; this solid, m. p. 51°, reliquefied on standing in a vacuum desiccator over sulphuric acid, indicating the presence of water of crystallisation; yield 20% (Found: C, 58·2; H, 7·5; H_2O, 9·3. $C_9H_{12}O_3,H_2O$ requires C, 58·0; H, 7·6; H_2O, 9·7%).

2-*p*-Bromophenoxyethanol (Shukis and Tallman, *J. Amer. Chem. Soc.*, 1944, **66**, 1461) gave a *p*-nitrobenzoate, m. p. 103°, white needles from alcohol (Found: N, 3·85. $C_{15}H_{12}O_5NBr$ requires N, 3·8%).

The author thanks the University of Sydney for a Research Scholarship, and members of the Department for their interest.—Department of Organic and Applied Chemistry, University of Sydney. [*Received, February 13th*, 1946.]

The Reduction of p-*Nitrobenzoic Acid to Hydrazo- and Azo-benzene-4 : 4′-dicarboxylic Acids by Means of Glucose.*

By Muriel L. Tomlinson.

It is well known that *p*-nitrobenzoic acid in alkaline solution is reduced by reagents such as sodium amalgam (Meyer and Dahlem, *Annalen*, 1903, **326**, 335) and sodium stannite (Goldschmidt and Eckardt, *Z. physikal. Chem.*, 1906, **56**, 404) to yield mixtures of azo- and azoxy-benzene-4 : 4′-dicarboxylic acids. Since the free acids are very insoluble substances which decompose at relatively high temperatures, and also since mixtures of their esters crystallise together and simulate pure substances, there was some confusion in the early literature about their identities. Meyer and Dahlem (*Annalen*, 1903, **326**, 331) give what have proved to be authentic descriptions of the acids and their ethyl esters.

Bacharach and Weinstein (*Rec. Trav. chim.*, 1935, **54**, 931) claim to have reduced *p*-nitrobenzoic acid in alkaline solution to azo- and azoxy-benzenedicarboxylic acids by the use of glucose, and they state that the production of the azo- or the azoxy-derivative depends only on the temperature at which the reaction takes place. They characterised their products merely by nitrogen and carboxyl determinations. Repetition of their processes showed that the mixtures, with which they started and which they described as solutions, contain much undissolved sodium *p*-nitrobenzoate, and that their so-called azo- and azoxy-acids gave esters differing in m. p. from those described by Meyer and Dahlem. Further investigation has shown that, under both of the sets of conditions described by Bacharach and Weinstein, the products are mixtures of hydrazobenzene-4 : 4′-dicarboxylic acid (I), first obtained by Bilfinger (*Annalen*, 1865, **135**, 159) and azobenzene-4 : 4′-dicarboxylic acid (II) (Meyer and Dahlem, *loc. cit.*). It has been shown that this reaction can be modified to give good yields of (I) and (II), but under none of the conditions investigated has the azoxy-compound been obtained using glucose as reducing agent. Catalytic reduction of (II) in alkaline solution yields *p*-aminobenzoic acid with the absorbtion of two mols. of hydrogen per g.-mol., but on similar treatment the products obtained by Bacharach and Weinstein's methods absorbed considerably less than four atoms of hydrogen per mol.

Hydrazobenzene-4 : 4′-dicarboxylic Acid (I).—*p*-Nitrobenzoic acid (13 g.) and sodium hydroxide (50 g.) were mixed in water (225 c.c.) and the solution was warmed to 50°. A solution of glucose (100 g. in 150 c.c. of water) was then added slowly at 50° and the mixture was warmed on a steam-bath until a precipitate started to form. It was then removed and well shaken; the liquid filled with a pale yellow precipitate which soon dissolved to give a brown solution. Air was excluded and the solution was cooled and acidified with acetic acid. The precipitate consistsed mainly of (I). It was extracted with hot glacial acetic acid, in which (II) is insoluble, and on cooling the solution deposited colourless needles, m. p. 286° (decomp.) (Found : C, 57·7; H, 4·7; N, 8·7. Calc. for $C_{14}H_{12}O_4N_2,C_2H_4O_2$: C, 57·8; H, 4·8; N, 8·7%). The acetic acid of crystallisation was removed by solution in air-free sodium hydroxide and precipitation with air-free hydrochloric acid (Found : C, 61·9; H, 4·7. Calc. for $C_{14}H_{12}O_4N_2$: C, 61·8; H, 4·4%).

Azobenzene-4 : 4′-dicarboxylic Acid (II).—The above process was repeated and then a stream of air was drawn through the brown solution for some hours, until no further precipitate of the sodium salt of (II) was formed; on acidification the mixture deposited (II) (yield, 8—9 g.). Hot potassium carbonate solutions of (II), on cooling, yielded orange needles of the *potassium* salt of (II) which was recrystallised from water (Found : C, 48·7; H, 2·5; N, 8·0. $C_{14}H_8O_4N_2K_2$ requires C, 48·6; H, 2·3; N, 8·1%). The acid (II) could not be recrystallised (Found : C, 62·2; H, 3·8; N, 10·6. Calc. for $C_{14}H_{10}O_4N_2$: C, 62·2; H, 3·7; N, 10·4%). Catalytic reduction of (II) was not effected, probably because of its insolubility, but aqueous sodium carbonate solutions of (II) were reduced to *p*-aminobenzoic acid (isolated as acetyl derivative) by hydrogen with palladium–charcoal [1 g. of (II) absorbed 182 c.c. of hydrogen at 15°. Calc. for 2 mols., 176 c.c.].

Azobenzene-4 : 4′-dicarboxyl Chloride (III).—This was referred to, but not described, by Einhorn and Uhlfelder (*Annalen*, 1909, **371**, 140); Uspensky's description (*J. Russ. Phys. Chem. Soc.*, 1891, **23**, 93) refers to a mixture of azo- and azoxy-compounds. The acid (II) was refluxed with excess of thionyl chloride for 24 hours, or (II) (1·7 g.) and phosphorus pentachloride (2·9 g.) were heated in *o*-dichlorobenzene (20 c.c.) for 15 minutes, and the precipitate obtained by dilution with light petroleum was recrystallised from light petroleum (b. p. 60—80°), from which *azobenzene-4 : 4′-dicarboxyl chloride* separated as red needles, m. p. 164° (Found : C, 55·1; H, 3·1. $C_{14}H_8O_2N_2Cl_2$ requires C, 54·7; H, 2·6%). The ethyl ester (IV), m. p. 143°, was obtained when (III) was warmed with alcohol, and the same ester was also obtained (*a*) by refluxing (II) with alcoholic sulphuric acid for 24 hours, and (*b*) when equal weights of ethyl *p*-aminobenzoate and ethyl *p*-nitrosobenzoate were heated in alcohol or acetic acid for 1 hour (Found : C, 66·0; H, 5·5; N, 8·6. Calc. for $C_{18}H_{18}O_4N_2$: C, 66·3; H, 5·5; N, 8·6%). An alcoholic solution of (IV) (0·3 g.) absorbed 48 c.c. of hydrogen at 23° in the presence of palladium–charcoal (calc. for 2 mols., 45 c.c.). Interruption of reduction when half of this quantity of hydrogen had been taken up yielded the ethyl ester of (I) as colourless needles, m. p. 120° (from alcohol) (Found : C, 65·4; H, 5·9. Calc. for $C_{18}H_{20}O_4N_2$: C, 65·9; H, 6·1%). Oxidation of (IV) with hydrogen peroxide in acetic acid for 24 hours at 100° gave ethyl azoxybenzene-4 : 4′-dicarboxylate identical by mixed m. p. determination with that prepared as described by Meyer and Dahlem (*loc. cit.*).

Ethyl p-*Nitrosobenzoate.*—(Cf. Alway and Pinckney, *Amer. Chem. J.*, 1904, **32**, 399.) Potassium persulphate (8 g.) was mixed with sulphuric acid (6 c.c.) and left for ½ hour. Ice (50 g.) was then added and the solution was neutralised with sodium carbonate crystals. Ethyl *p*-aminobenzoate (2·5 g.) in water (300 c.c.) was added and the solution was left overnight. The precipitate was filtered off, dissolved in ether, and washed with dilute acid; ethyl *p*-nitrosobenzoate was obtained by steam distillation of the residue left after evaporating the ether (Found : C, 60·4; H, 5·0. Calc. for $C_9H_9O_3N$: C, 60·3; H, 5·0%).

M. p.s are uncorrected.

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OBITUARY NOTICES.

REGINALD GRAHAM DURRANT.

1859—1945.

REGINALD GRAHAM DURRANT, who died on Oct. 4th, 1945, was one of the oldest members of the Chemical Society, both in terms of years and length of fellowship, since he became a Fellow of the Society in 1883. He was born on Jan. 22nd, 1859, at Halesworth, Suffolk, one of the family of five sons and two daughters of the Rev. R. N. Durrant. He was educated at Taunton and Keble College, Oxford, which he entered with a science scholarship. After graduating in 1882 he worked for a year at Mason College, Birmingham, under Dr. (later Sir William) Tilden. He went to Marlborough College in 1883 as a temporary master and was appointed to the staff of assistant masters in the following year, remaining at Marlborough until his retirement in 1919. At the commencement of this long period he was probably the only science teacher at Marlborough, but at the end of it there were more than ten. There can be little doubt that his keenness and ability and capacity for interesting, not only his pupils, but others in scientific matters were in large measure responsible for this great increase in the science teaching at Marlborough. In 1919 he joined University College, Reading, as a lecturer in Chemistry and remained there and at the University of Reading, latterly as Honorary Research Fellow, until 1940. War-time difficulties, rather than lack of energy or inclination, led to his final retirement from active chemistry in that year when he went to live with his sister, first in Wales and then in Torquay. He had a slight stroke about Christmas 1944 and returned with his sister to his old house in Marlborough a few months before his death.

Durrant had an unusual personality and one which endeared him to young and old alike. Though he was never married he would have made an ideal husband and father. Many generations of schoolboys and students had passed through his hands, including many who subsequently became eminent in various walks of life, and all remember him with affection. His keenness and enthusiasm were infectious. Dr. Ulick Evans writes, " He was a good friend to whose kindness I owe very much. More than anyone else he gave me a taste for scientific *exploration* into new fields—as opposed to the detailed *survey* of fields already roughly known."

Durrant's approach to his work was essentially that of the explorer, and in 1903 he did a little mild exploration in the geographical field, visiting two brothers in South Africa and trekking with them with bullock cart from Johannesburg to Victoria Falls before the days of the railway.

He had many open air interests, more particularly fly-fishing, golf, and water colour sketching. He helped to lay out the links at Poldhu in Cornwall and that on Marlborough Common, while fly-fishing and sketching played an important part in all his holidays. The writer well remembers a long tramp in the Berwyn Hills, when after lunch in the heather Durrant brought out his sketch book and in a surprisingly short time had produced a very pleasing picture. He must have made hundreds of sketches in this way. Their production gave him great satisfaction and they were attractive to others, for he had a keen eye for scenery and no mean ability in recording it. His interest in colour led him in later years to a process for colouring roofing slates by means of metal hydroxide sols but, although this appeared promising, it never became commercially successful.

Durrant had very wide interests, a keen sense of humour, and a good fund of stories and anecdotes largely from his own experience. He was essentially human and very unselfish. His remembrances and stories of other people were always kind, and as he was a generous and delightful host it is not surprising that he was much sought after and always welcome at all social gatherings. He was a keen bridge player.

He was a born experimenter and a good example of the schoolmaster who had always kept alive his interest in research. While at Marlborough he managed to find time for several investigations and published papers in the *Journal* on green compounds of cobalt produced by oxidising agents (1905, also notes on the same subject in the *Proceedings* for 1896); the action of stannous chloride on sulphuric acid and on sulphurous acid (1915); and the interaction of stannous and arsenious chlorides (1919). A paper on ionic migration in the natural diffusion of acids and salts published in the *Proceedings of Royal Society* (1906) describes interesting experiments on diffusion in jellies and concentrated solutions without the use of jellies. One theoretical paper on the numerical relation of atomic weights to atomic numbers was published in the *Journal of the American Chemical Society* (1917). At Reading he was able to exercise this bent for research to the full, and during the twenty years he spent there he almost lived in his laboratory and was an inspiration to younger men. He carried out in collaboration with the writer a series of investigations which were published in the *Journal*. These were on the action of ammonium nitrate and of aqueous ammonia on copper, and properties of cupric tetrammine nitrite and nitrate (1922); the action of thiosulphates on cupric salts (1923); the interrelationships of the sulphur acids (1927); colloidal sulphur (1931); and equilibria and changes in metal hydroxide sols (1942). His approach to these problems was often novel and led to results of importance.

His long life was a happy one and well spent.

H. BASSETT.

JAMES HART-SMITH.

1877—1946.

JAMES HART-SMITH was born in London and received his early education at Berkhamsted School, from where he obtained scholarships both to Christ's College, Cambridge, and to the Royal College of Science. He accepted the latter, and in due course qualified for the Associateship of the Institute of Chemistry. He continued at the Royal College for two years as a Demonstrator in Chemistry, and collaborated with the late Sir Martin Onslow Forster on work in the terpene field, particularly on the isolation and characterisation of neobornylamine (*J.*, 1900, **77**, 1152). Subsequently he was engaged for another two years teaching science at Hinckley Grammar School, Leicestershire.

In 1902 he joined the staff of Battersea Polytechnic where he served as Senior Assistant Master and Senior Science Master at the Boys' School. This school was originally an integral part of the Polytechnic, but during his 26 years' service it developed and flourished so vigorously that ultimately it split off from the parent body and became the Henry Thornton School with premises at Clapham Common.

Hart-Smith's chemical activities were not confined solely to teaching. In 1918 he published "Recent Discoveries in Inorganic Chemistry," and it is characteristic of the author that a chapter on radio-activity had to be omitted because of the heavy weight of extra war-work which he had undertaken whilst the book was in preparation.

Hart-Smith retired from teaching in 1937, but remained a busy and active man. The treasurership of the Secondary School Teachers' War Relief Fund, which he had accepted at the inauguration of the Fund in 1916, he retained until 1945, and he was in addition for many years a member of the British Social Hygiene Council, and of the Council of the Safety First Association.

He was residing at Bournemouth at the outbreak of war in 1939, and immediately attempted to obtain some chemical war-work. This he found very difficult on account of his age, his attempts, for instance, to obtain employment in a cordite works being frustrated by the fact that he was seven years older than the maximum age allowed. When the air-raids started, however, he became one of the Head Fire Guards for Bournemouth, and later, with the help of his wife, founded and maintained the Southbourne National Savings Centre.

When the war ended, Hart-Smith looked forward keenly to the opportunity of resuming the photographic studies in which he had long been interested. In 1946 he went to Seaford for his first holiday since 1939. The sea wall had recently been severely damaged by heavy gales; when attempting to photograph the damage, he became dazzled by the glare of the sun from the sea, and slipped from the wall, receiving severe injuries which subsequently proved fatal.

No account of Hart-Smith's career would be complete without reference to the influence which he exerted on the many generations of pupils who passed through his hands whilst he was a chemistry master at Battersea. In his teaching he united a fine gift of exposition with an exceptional ability for inspiring interest in his subject. These qualities, combined with his very kindly although firm manner, gave a most stimulating atmosphere to his classes, and the many Fellows of our Society who were fortunate to be his pupils look back on Hart-Smith with gratitude and affection.

F. G. MANN.

HERBERT INGLE.

1861—1945.

HERBERT INGLE was one of the first chemists trained at the Yorkshire College of which he became an Associate by examination in 1880 before the University of Leeds received its charter, but in a period when A. H. Green, A. W. Rücker, T. E. Thorpe, and L. C. Miall were already, as professors of science, staking out claims for its future. Following on a notable career as a student, he became a member of the staff of the Department of Chemistry, and successive generations will remember gratefully their introduction to laboratory work at his hands. Brought up on a farm, with first-hand knowledge of its working, he became an obvious choice for a newly instituted lecturing post at Leeds in the then obscure subject of Agricultural Chemistry, on which he wrote a text-book. When, at the end of the Boer War, Milner gathered round him a staff of experts for the administration of South Africa, Ingle was appointed Agricultural Chemist for the Transvaal. This was useful and interesting work, but was terminated by the retrenchment which followed the grant of self-government, and he returned home. Then followed a new kind of activity. With the support in succession of two Leeds citizens, John Bray and Robert Armitage, he engaged on the preparation of pure solid extracts of coffee and tea, bringing the process to successful issue. This was his main professional interest up to the time of his death on Oct. 27th, 1945. He had married Alice Roddis of Birmingham who died only a few weeks before him; two daughters and a son survive him. He had become a Fellow of the Chemical Society in April, 1889, a Fellow of the Institute of Chemistry in 1888, and had been granted the B.Sc. degree in 1905 when the University of Leeds received its charter.

Herbert Ingle's varied career was rendered possible by an unusual combination of scientific knowledge and the faculty for its application. On any problem which presented itself his judgment was almost invariably

sound and often refreshingly independent. This was well known to a limited circle, but a very much wider, more public reputation would have been his if he had not estimated so highly the privileges of privacy and been so apt to think that what was obvious to himself was the same to others, needing no explanation and least of all public explanation. I write as an early student of his and a friend of long standing. The same preference for privacy was displayed in his choice of the perfect holiday, which meant for him rock-climbing in the Lake District with a few trusted companions.

JOHN W. COBB.

WILLIAM JAMES COLTART ORR.

1911—1946.

WILLIAM JAMES COLTART ORR was born in Edinburgh on 23rd December, 1911. After a preliminary schooling in Ireland, he was educated in Dunbar Secondary School and Ayr Academy, from which he entered Edinburgh University in 1929 as an Ayr County Scholar. He graduated with First Class Honours in Chemistry in 1933, being first of his year, and was thereupon awarded a Carnegie Scholarship, which enabled him to return to the University for research under the supervision of the writer. For his researches, which were concerned with the reactions of heavy water with various organic substances and with the diffusion of deuterium hydroxide in water, he was awarded the Ph.D. degree in 1935. At this period his strong leaning towards theoretical investigation showed itself and he also made an analysis of the factors determining the electrolytic dissociation of salt molecules in water (*Phil. Mag.*, **1934**, **18**, 778).

In 1936, having been awarded a Carnegie Research Fellowship, he went to the Colloid Science Laboratory at Cambridge to work under the supervision of Professor E. K. Rideal and the late Dr. J. K. Roberts. His first research there was an examination in detail, both experimentally and theoretically, of the behaviour of simple non-polar molecules adsorbed on ionic salt lattices. The degree of Ph.D. (Cantab.) was conferred on him in 1939.

From 1939 to 1941 he held an 1851 Exhibition Senior Research Studentship, during part of the tenure of which he was engaged in confidential work for the Air Ministry and Ministry of Supply. Part of this work has been published (*Trans. Faraday Soc.*, 1941, **37**, 587) in a paper on isotopic separation by fractional crystallization. During this period he also began experiments on the thermodynamic behaviour of gases, such as hydrogen, helium, and neon, at low temperatures, but owing to the prevailing conditions they were not completed. His theoretical work was continued in a paper on the determination of internal energies by inductive analysis (*Proc. Camb. Phil. Soc.*, 1942, **38**, 224) and in a continuation of his work on the factors determining electrolytic dissociation (*Phil. Mag.*, 1941, **31**, 51). He also contributed a general review on the subject of intermolecular energies to the Annual Reports of the Chemical Society.

From 1941 to 1945 he was a research chemist with the British Rubber Producers Research Association, and carried out for them both theoretical and experimental researches on the thermodynamic behaviour of polymer–solvent systems. Two papers on this work have been published (*Trans. Faraday Soc.*, 1944, **40**, 306, 320) and two more are in course of publication. The last (with Dr. G. Gee) gives experimental data for the system natural rubber–benzene and contains the most reliable data so far obtained on the dependence of heats of mixing on concentration.

In October, 1945, Orr returned to Scotland as an I.C.I. Fellow in the University of Glasgow. He had begun his work there and was enthusiastically settling down to a programme of teaching and research, when he was stricken with influenza from the effects of which he died on March 13th, 1946. By his early death the country is deprived of a combination of mathematical and experimental ability which is all too rare, at a time when it had just reached its full maturity. Having a critical and cautious attitude, he was not satisfied until he got to the bottom of his problems, and his papers show a willingness to spend time clearing up fundamental points before attacking the more complex problems. Kindly and unassuming, he was always ready to help his colleagues and fellow students, and when his help was asked no trouble was too much for him to take.

J. A. V. BUTLER.

WILLIAM POLLARD.

1870—1946.

WILLIAM POLLARD was a Fellow of the Chemical Society for forty-eight years and, although he retired from the Geological Survey in 1913 on account of ill-health, he maintained a lively interest in scientific matters until within a few weeks of his death.

After leaving Harrow in 1888, he spent six months in Dresden and then proceeded to Gonville and Caius College, Cambridge. He has been described as an enthusiastic undergraduate who with Professor Arthur Hutchinson (then a research worker in the college laboratory) carried out useful work on the preparation and nature of lead tetra-acetate and explored the possibilities of the preparation of other salts of quadrivalent lead (*J.*, 1893, **63**, 1136; 1896, **69**, 212).

From Cambridge he went to Tübingen University where he worked under Professor Lothar Meyer and

obtained his doctor's degree in 1894 for his work on the estimation of molybdic acid and the determination of the atomic weight of molybdenum.

He returned to Cambridge and continued to work in the Caius laboratory where he collaborated with Mr. Pattison Muir and Dr. R. S. Morrell, until in 1898 he was appointed chemist (nominally a geologist) to the Geological Survey. In spite of few facilities for laboratory work in the Jermyn Street museum at that time, he carried out many useful analyses of silicate rocks and minerals, and made a systematic study of South Welsh Coals, which contributed to knowledge of the processes of formation of anthracite. He later transferred his attention to the study of rare earths. From 1901 to 1913 he was in charge of the new chemical laboratory at Jermyn Street, and he trained E. G. Radley who came to him from a technical post at Dulwich College, so that he in turn was responsible for much valuable analytical work.

During the 1914—1918 war, in spite of heart trouble, Dr. Pollard carried out investigations on gas protection in Cambridge and at his private laboratory at Oakfield, Hitchin. His valuable services as a voluntary worker to the Chemical Warfare Committee received official appreciation from the War Office and the Army Council.

Dr. Pollard's enthusiastic interest in many aspects of chemistry and his entertaining reminiscences of various laboratory incidents and contretemps with railway officials about the transport of dangerous chemicals were most stimulating to his companions. It was a great pleasure while staying at his home to listen to his accounts of his own experiences and of those of his chief associates, who, besides those already mentioned, included Professor J. Stanley Gardiner and Edward Wilson of the Antarctic.

In 1903 he married Georgina Evelyn, only child of the Reverend George Potticary, late Rector of Girton, Cambridge. He is survived by his widow and three sons. He was a keen shot until his eyesight gave him trouble, and he was also an efficient amateur photographer. He found the recent war a great strain, particularly as he was not well enough to work himself, although he followed scientific developments with keen interest.

For information of Dr. Pollard's work at Cambridge, the writer is indebted to Dr. R. S. Morrell of Wolverhampton; and for details of his work on the Geological Survey to Dr. Hallimond and to Sir John Flett's History of the First Hundred Years of the Geological Survey of Great Britain.

F. M. F. Thomas.

ALEXEJ EUGUENIEVITSCH TCHITCHIBABINE.

1871—1945.

On August 15th, 1945, died in Paris the celebrated Russian chemist Alexej Euguenievitsch Tchitchibabine (Tschitschibabin), who was born at Kusemino, near Poltava, on March 17th, 1871.

From 1888 to 1892 Tchitchibabine studied at the University of Moscow. While still a student he made his first communication to the chemistry section of the Society of Natural Science at Moscow. The first steps of his career, however, were not easy. At first the very independence of his character and originality of his mind told against him: for he directed his first researches to pyridine chemistry, a field at that time little known, and apparently of so little interest that, in the eyes of some of his teachers, this choice was a token of mediocrity. But Tchitchibabine was not deterred either by their discouraging advice or by the material difficulties in which he found himself, and he forged ahead with the task which he had set himself.

He obtained a science degree from the University of Moscow in 1892, and in 1902 he was appointed "Magister Chimia" at Moscow after having presented a thesis on the effect of alkyl halides on pyridine and quinoline. Later he was made a Doctor of Chemistry of the University of St. Petersbourg, in Russia a rare honour. In 1908 he was appointed Professor of Organic Chemistry at the Imperial College of Technology of Moscow, and from 1909 to 1929 he was Dean of the Faculty of Chemistry of this College; from 1918 to 1923 he was also Professor of Chemistry at the University of Moscow.

During the first world war he directed his energies to the organisation of the pharmaceutical chemical industry of Russia. Thanks to his efforts, in the face of extreme difficulties, Russia was soon manufacturing a large number of chemical products (in particular alkaloids) which had previously all been imported from Germany.

From 1931 until his death, Tchitchibabine lived in Paris where he had been given a laboratory at the Collège de France.

Tchitchibabine published more than 250 papers in various fields of organic chemistry. The majority deal with pyridine chemistry. In his researches directed towards a synthesis of compounds having a pyridine nucleus, he studied the condensation of aldehydes and ketones with acetylene and ammonia and showed that while at a moderate temperature (180°) under pressure α-substitution derivatives are obtained, at higher temperatures (about 400°) under normal pressure and with catalysts the synthesis will give γ-derivatives (*e.g.*, γ-picoline). By using different aldehydes (or ketones) it was thus possible to obtain very varied derivatives, and by employing a mixture of acetaldehyde and acrolein Tchitchibabine achieved the synthesis of pyridine itself. One of his last achievements was that of modifying the synthesis of quinoline by substituting acrolein for glycerol.

In 1913 Tchitchibabine and his co-worker Seide made the remarkable observation that sodamide acts on pyridine and its derivatives, giving good yields of aminopyridines (in particular, the α-aminopyridines). This discovery was of major importance in the development of pyridine chemistry since the introduction of the

amino group greatly activated the pyridine nucleus. The phenomena of tautomerism in the amino-pyridines and -picolines observed and studied by Tchitchibabine and his collaborators also increased the theoretical interest and the variety of possible applications of this work. Again, by studying the action of alkyl halides on sodium derivatives of picoline, Tchitchibabine succeeded in obtaining higher homologues of pyridine.

His fundamental work on pyridine chemistry, a subject which has been gaining in importance ever since, led to the synthesis of a great variety of natural products, pharmaceutical chemicals, etc. Tchitchibabine's research was not, however, confined to this field; he did outstanding work in other branches of chemistry. At the beginning of the century he carried out extensive research on the problem of tervalent carbon, and in 1912 he was invited to England by the British Association to lecture on this subject. There were, too, his investigations of the composition and synthesis of various alkaloids and other plant products (pilocarpine, santonin, bergenin, etc.), his work on the alkylation of phenols in the presence of various condensing agents, in particular phosphoric acid, his study of new reactions with organomagnesium compounds which led to methods of synthesis of acetals and alkoxy-ethylenic acids, and his study of naphthenic acids from Russian oils. We also owe to him the synthesis of thiodiglycol from ethylene oxide and hydrogen sulphide.

In 1924 appeared in Russia his treatise " Basic Principles of Organic Chemistry " which has been revised several times and also translated into French. As we open the book we read : " To the memory of Natacha Tchitchibabine, my beloved daughter, my ablest assistant and my best friend, I dedicate my life's work." Natacha, his only child, also a chemist, was killed in 1930 in an explosion in a chemical products factory.

Tchitchibabine was fortunate in having by his side, throughout his brilliant but arduous career, his wife Vera Vladmirovna Tchitchibabine, also a scientist, whom he had known from her schooldays.

I. MARSZAK.

KAPILRAM HARDEVRAM VAKIL.

1884—1946.

MR. KAPILRAM HARDEVRAM VAKIL was born in Surat (India) on 28th May, 1884, of a family of lawyers, and was a grandson of the late Mr. Nanabhai Haridas, the first Indian Judge of the Bombay High Court. He was educated at Bharda New High School, Bombay, Elphinstone College, Bombay, and Manchester College of Technology. He passed the B.A. examination of the University of Bombay in 1906, and was awarded the Bell Prize in Physics. He proceeded to England in 1909 for further studies and obtained the B.Sc. (Tech.) degree of the University of Manchester with First Class Honours in dyeing, bleaching, and oils and fats. On his return to India he joined the Jamshed Oil Mills of Tatas at Kurla as manager and consulting chemist and did the pioneering work of developing the cotton-seed oil industry in India. Later, he started independent consultant practice and helped a number of industrial concerns with his technical advice.

He was greatly interested in research work from the beginning of his career, and his first paper, on the chemical examination of ghee, was published in 1915 (*J. Soc. Chem. Ind.*, **34**, 320). He had invented and was the patentee of several processes for refining oils and fats. During the First World War he proceeded in 1916 to the Manchester College of Technology and was awarded the Manchester Corporation special research scholarship. During this period he carried out, in collaboration with Prof. Green, research work on the sulphonation of β-naphthylamine which was published in the *Journal* (1918, **113**, 35). While he was in England he read an important and valuable paper on cotton-seed products before the Manchester Branch of the Society of Chemical Industry which was subsequently published (*J. Soc. Chem. Ind.*, 1917, **36**, 685). He was awarded the M.Sc. (Tech.) degree of the University of Manchester in 1917 and was also admitted to the Associateship of the Institute of Chemistry, of which he became a Fellow later. He received an offer of the Privy Council Scholarship for continuing research work at Manchester and was invited by Lever Bros. to act as their consultant in the East, but he preferred to join the Tatas as consulting chemist and in this capacity he carried out surveys and research work on a number of important industrial problems.

Early in his career, Vakil had realised the great importance of establishing key chemical industries—particularly the alkali industry—in India, and his whole life was devoted towards the achievement of this ideal. As early as 1917, he carried out extensive surveys for a suitable site for salt works on the Eastern coast of India for the then proposed heavy chemicals, etc., industries of Tatas at Sakchi (now Jamshedpur), and in 1920 he investigated the prospects of establishing an alkali industry at Kodinar in Kathiawar. In this connection he was also deputed by Tatas in 1920—1921 to visit the various alkali works in Europe and America, and had discussions and consultations with a number of well-known alkali experts. In 1923 his services were engaged by Dhrangadhra State (Kathiawar) for their soda-ash project which he successfully completed, and in 1926 he started the Okha Salt Works at Mithapur, where he carried out his pioneering work of recovering and manufacturing important by-products from bitterns. In 1937 the Tatas accepted his scheme for establishing the heavy chemicals industry at Mithapur (Kathiawar), and Tata Chemicals, Limited, was finally started in 1939 with Vakil as Technical Director. Tata Chemicals is the largest chemical concern in India and is the crowning glory and fulfilment of his life's mission.

Vakil was a member of a number of scientific societies, and had the distinction of being the first Indian to be elected directly to the full membership of the Institute of Chemical Engineers and also to the membership of the Society of Public Analysts. He contributed a number of original papers to scientific journals and is the

author of two authoritative books on salt and Indian coal. His advice was sought by a number of organisations and he served on a large number of important Government and other Committees. He was held in the highest esteem by his friends, colleagues, and subordinates, and the Government of Baroda bestowed on him the high honour of Raj Ratna in recognition of his services in developing the salt industry in the State.

Vakil was a very widely travelled man and had visited foreign countries a number of times. In his early days he was an active member of Indian National Congress, but on the advice of Mahatma Gandhi left politics and devoted his whole attention to the development of chemical industries in India. To attain his long cherished goal of putting India on the industrial map of the world he spared no pains and lived the life of a recluse wholly devoted to work. As a result of long and continuous hard work his health broke down last year and he was advised to rest. He, however, was so devoted to work that he disregarded the advice of his physicians and died in harness on 29th January, 1946, through heart failure. His death has been a great loss not only to his family and friends, but also to India, who has lost by his death one of her ablest and most eminent technical chemists and chemical engineers.

N. A. YAJNIK.

ERNEST ADAM WAGSTAFF.

1907—1942.

PILOT OFFICER ERNEST ADAM WAGSTAFF was shot down over France on October 25th, 1942, and lies, with his air-crew, buried at Moulin-sur-Touvent some 25 miles N.E. of Paris.

He was educated at Nottingham High School and the University College of Nottingham. As an undergraduate, although his physical presence was conspicuous his reticence and diffidence made him little known. As a research student it was otherwise. After a short spell in a sugar beet factory he returned to the college to engage in research in organic chemistry. A little the senior of the other students and a lot taller he assumed a station *in loco parentis*, his former diffidence vanished and his strikingly original character revealed itself. He studied the nitration of β-phenylethyl-, styryl-, and phenylacetylenyl-pyridines and, as one of his contemporaries remarked, " he nitrated stilbazole with a zeal which was at once an example to, and the wonder of, us all." The results of the work were published in four papers in the *Journal*.

Wagstaff's enthusiasm for organic chemistry was not born of a narrow-minded lack of interest in all else. He was well acquainted with all branches of chemistry and had not a litlte knowledge of botany and geology. Outside science his interests ranged from mediaeval alabaster carvings and windmills to Norman castles in Pembroke and Iron-Age camps in Dorset, from the operettas of Gilbert and Sullivan to the writings of Belloc, Chesterton, and A. E. Housman. He was an excellent shot with both the ·22 and the service rifle, and was a member of the winning Nottingham Team in the Inter-Universities Small-Bore Championship. He walked extensively both in this country and on the continent and attended the Sixth International Congress of Agricultural Chemists at Budapest in 1939.

As a writer of letters he was inimitable and could express himself as readily in verse as in prose; in choice of word and turn of phrase he was always original and often strikingly effective.

After obtaining the degree of Ph.D. of London University Wagstaff joined the Research Department of the Distillers Company in January 1933. From 1934 to 1937 he was in charge of the Molasses Control Laboratory. From April 1937 until he joined the Royal Air Force as a volunteer he was one of a team of workers engaged in process development work in connection with a vapour-phase catalytic oxidation reaction.

It may have been the repeated bombing to which he was subjected whilst engaged in the erection of a chemical plant that induced him, in October 1940, to enlist in the Royal Air Force. He did not analyse his motives to others but said later that he did not regret his decision except insofar as his action made others restless. Writing from " the quiet of an R.A.F. training camp " he said that, hearing of the trials under bombing of those left behind in his former job, he felt " something of a shirker." He made friends in the R.A.F. and seemed to enjoy barrack life for its own sake. After training in this country and in North America he was commissioned in April 1942, and saw much of the Britain he loved before those inimitable letters, coming now from an aerodrome in Lincolnshire, suddenly ceased.

Wagstaff's original work was, for the most part, not for publication; this circumstance, together with his untimely death, prevented him from making for himself a name in chemistry commensurate with his talents. He died, as he had lived, for an ideal; in the lives of the few who knew him well his passing leaves a void which can never be filled.

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